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TITLE: Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women

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| 14. ABSTRACT<br>The purpose of this Minority Institution Partnership Training Award is to train University of Texas at Brownsville (UTB) faculty to conduct breast cancer research by collaborating with faculty from the University of Texas-Houston School of Public Health (UTSPH). Three UTB faculty will undergo intensive training provided by six UTSPH faculty during year 1. To reinforce training, faculty from UTB and UTSPH will conduct a clinic-based case-control study of breast cancer to investigate its' association with hormones, diet and body size in years 2 through 4. Specific aims include: 1) to provide UTB faculty training through classes, presentations and seminars to gain knowledge of epidemiology, proposal development, behavioral sciences, and biostatistics offered by UTSPH faculty, and 2) to design and conduct a clinic-based case-control study to include completion of a questionnaire, anthropometry and a blood draw. During the fourth year of the project, data collection continued for the clinic-based case-control study, the South Texas Women's Health Project. To increase the number of breast cancer cases, we attempted to include Hidalgo county by teaming up with an investigator from the University of Texas Medical Branch. Dr. Sanderson (UTSPH) continued in her role as principal investigator of a project funded by the National Center on Minority Health and Health Disparities to conduct a study of women diagnosed with high risk-human papillomavirus which places them at high risk of cervical cancer, and as principal investigator of a grant from the Texas Cancer Council to investigate the utility of electronic pathology lab reporting the to the Texas Cancer Registry on the Texas-Mexico border. Dr. Sanderson (UTSPH) and Dr. Nair (UTB) submitted a Synergistic Idea Award application to conduct a substudy of the South Texas Women's Health Project to investigate genes associated with obesity and diabetes. |             |                                  |                            |                                              |                                           |
| 15. SUBJECT TERMS<br>Epidemiology/biostatistics, nutrition, hormone metabolism                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |             |                                  |                            |                                              |                                           |
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## **Introduction**

The purpose of this Minority Institution Partnership Training Award is to train University of Texas at Brownsville (UTB) faculty to conduct breast cancer research by collaborating with faculty from the University of Texas-Houston School of Public Health (UTSPH). Three UTB faculty will undergo intensive training provided by six UTSPH faculty during year 1. Additional training will take place in subsequent years. To reinforce training, faculty from UTB and UTSPH will conduct a clinic-based case-control study of breast cancer to investigate its' association with hormones, diet and body size in years 2 through 4. Specific aims are: 1) to provide UTB faculty training through classes, presentations and seminars to gain knowledge of epidemiology, proposal development, cancer epidemiology, intervention mapping, field epidemiology, biostatistics, and nutrition epidemiology offered by UTSPH faculty in-person from Brownsville and via ITV from Houston, 2) to design and conduct a clinic-based case-control study to include completion of a questionnaire, anthropometry and a blood draw, 3) to disseminate findings to the Texas Department of State Health Services, the Department of Defense, and local health providers and health clinics, and 4) to submit proposals to conduct larger population-based case-control studies of breast cancer in the Lower Rio Grande Valley.

## **Body**

This project is occurring in two phases, the training phase (year 1) and the investigation phase (years 2 through 4). The only training task that was fully completed during the first year of the project was training task 5. The training tasks that were fully completed during the second year of the project were training tasks 4 and 6. The training task that was fully completed in the third year of the project was training task 1 when Dr. Peltz (UTB) received his master's of Public Health (MPH) degree. Since receiving his MPH, Dr. Peltz (UTB) published his master's thesis in Archives of Medical Research, and submitted abstracts from his leptin project funded by the University of Texas Health Science Center at San Antonio to two conferences. Although Dr. Johnson (UTB) will not earn a Master's of Public Health degree he audited advanced epidemiology in Fall 2006, and spent Spring 2007 evaluating psychometric measures of acculturation. During the fourth year of the project, we further completed training task 2 by Dr. Sanderson (UTSPH) continuing to receive funding from the Texas Cancer Council to investigate the possibility of utilizing electronic pathology lab reporting to the Texas Cancer Registry on the Texas and Mexico sides of the border. We further completed training task 3 by attempting to include Hidalgo county by teaming up with an investigator from the University of Texas Medical Branch (we obtained institutional review board (IRB) approval from the University of Texas Medical Branch on May 18, 2007 and are in the process of obtaining Department of Defense IRB approval to add this study site). We further completed training task 7 by obtaining continuing IRB approval from the University of Texas at Brownsville on March 29, 2007 (IRB of record for Valley Regional Medical Center is pending), from the University of Texas Health Science Center at Houston on July 31, 2007 (IRB of record for Harlingen Medical Center), from the Department of Defense on August 21, 2007, from the Texas Department of State Health Services on January 23, 2007, and from Valley Baptist Medical Center-Harlingen on July 31, 2007. We further completed training task 8 by attempting to revise the study design to include an additional study site in Hidalgo county.

During the fourth year of the project we continued in the investigation phase of the project by conducting a clinic-based case-control study. The primary purpose of the South

Texas Women's Health Project is to investigate the association between insulin resistance and breast cancer risk among Mexican American women. Eligible cases identified by surgeons and oncologists are Mexican American LRGV residents, aged 30-79, whose breast cancer is histologically confirmed. Two groups of controls with no history of breast cancer in a 4:1 control:case ratio are selected from the same location where the case received her diagnostic mammogram. The high-risk group consists of women receiving diagnostic mammograms, and the low-risk group consists of women who have no family history of breast cancer, no history of biopsy, and negative screening mammograms for the past two years. Trained interviewers conduct personal interviews to obtain information on demographics, lifestyle factors, personal health history (e.g., Type 2 diabetes), medication history (e.g., estrogen, non-steroidal anti-inflammatory drugs, and diabetic medications), menstrual and pregnancy history, family history of cancer and other chronic diseases, and adult weight history, and obtain the following anthropometric measurements: standing and sitting height, weight, waist and hip circumference, and body fat content. We are also collecting blood and performing assays to assess levels of hormones such as insulin and glucose and growth factors such as IGF-I associated with diabetes, obesity and breast cancer. Interviewing for the project began in January, 2004 and will continue through August, 2008. We anticipate obtaining information and blood samples from a total of 200 breast cancer cases and 1000 controls. Table 1 provides response rates to the interview and blood sample collection as of September 27, 2007.

| <b>Table 1. Response rates to the interview and blood sample collection for the South Texas Women's Health Project</b> |                      |          |                                   |          |                                  |          |
|------------------------------------------------------------------------------------------------------------------------|----------------------|----------|-----------------------------------|----------|----------------------------------|----------|
|                                                                                                                        | <b>N</b>             | <b>%</b> | <b>n</b>                          | <b>%</b> | <b>n</b>                         | <b>%</b> |
| <b>Interview</b>                                                                                                       | <b>Cases (n=158)</b> |          | <b>High-risk Controls (n=540)</b> |          | <b>Low-risk Controls (n=547)</b> |          |
| Refused                                                                                                                | 2                    | 1.3      | 27                                | 5.0      | 87                               | 15.9     |
| Lost                                                                                                                   | 1                    | 0.6      | 11                                | 2.0      | 18                               | 3.3      |
| Pending                                                                                                                | 3                    | 1.9      | 18                                | 3.3      | 14                               | 2.6      |
| Completed                                                                                                              | 152                  | 96.2     | 484                               | 89.6     | 428                              | 78.2     |
| <b>Blood sample</b>                                                                                                    | <b>Cases (n=154)</b> |          | <b>High-risk Controls (n=501)</b> |          | <b>Low-risk Controls (n=442)</b> |          |
| Refused                                                                                                                | 10                   | 6.5      | 12                                | 2.4      | 20                               | 4.5      |
| Lost                                                                                                                   | 0                    | 0.0      | 4                                 | 0.8      | 7                                | 1.6      |
| Began treatment                                                                                                        | 69                   | 44.8     | 0                                 | 0.0      | 0                                | 0.0      |
| Pending                                                                                                                | 0                    | 0.0      | 83                                | 16.6     | 57                               | 12.9     |
| Provided                                                                                                               | 75                   | 48.7     | 402                               | 80.2     | 358                              | 81.0     |

We further completed investigation task 1 by recruiting 152 women with breast cancer (96.2% of eligible breast cancer cases), 484 women receiving diagnostic mammograms (89.6% of eligible high risk controls), and 428 women receiving screening mammograms (78.2% of eligible controls) as of September 26, 2006 (see Table 1). Of respondents, blood has been drawn on 75 women with breast cancer (48.7% of responding breast cancer cases), 402 women receiving diagnostic mammograms (80.2% of responding high risk controls), and 358 women receiving screening mammograms (81.0% of responding low risk controls). We further completed investigation task 2 by conducting in-person and telephone interviews on breast cancer risk factors. We further completed investigation task 3 by collecting anthropometric

measurements, blood and urine. We further completed investigation task 4 by abstracting medical records for breast cancer screening, diagnosis and treatment. We further completed investigation task 5 by processing and storing blood and urine samples. We further completed investigation task 6 by completing enzyme-linked immunosorbent assays on hormones and growth factors. We further completed investigation task 7 by completing high-performance liquid chromatography analysis for urinary phytoestrogen. We further completed investigation task 8 by entering data for all questionnaires and assays. We further completed investigation task 9 by performing interim statistical analysis to assess data quality, and by Dr. Sanderson (UTSPH) presenting preliminary findings at 2<sup>nd</sup> Annual Texas Conference on Health Disparities in Fort Worth, Texas in June 2007. Tables 2 and 3 provide preliminary data on the South Texas Women's Health Project as of September 27, 2007. In comparison with controls, cases tend to be older, less educated, unmarried, and of lower socioeconomic status (see Table 2).

**Table 2. Preliminary comparison of cases and controls for demographic characteristics in the South Texas Women's Health Project**

| Characteristic    | Cases (n=151) |      | Controls (n=893) |      |
|-------------------|---------------|------|------------------|------|
|                   | n             | %    | n                | %    |
| Age (years)       |               |      |                  |      |
| 30-49             | 57            | 38.3 | 380              | 42.7 |
| 50-64             | 70            | 47.0 | 422              | 47.4 |
| 65-79             | 22            | 14.8 | 88               | 9.9  |
| Missing           | 2             |      | 3                |      |
| Language          |               |      |                  |      |
| English           | 76            | 50.3 | 467              | 52.3 |
| Spanish           | 75            | 49.7 | 426              | 47.7 |
| Educational level |               |      |                  |      |
| Grades 1-8        | 59            | 39.6 | 350              | 39.8 |
| Grades 9-11       | 28            | 18.8 | 116              | 13.2 |
| High school       | 25            | 16.8 | 155              | 17.6 |
| Some college      | 28            | 18.8 | 157              | 17.9 |
| College or more   | 9             | 6.0  | 101              | 11.5 |
| Missing           | 2             |      | 14               |      |
| Marital status    |               |      |                  |      |
| Married           | 93            | 61.6 | 618              | 69.3 |
| Unmarried         | 58            | 38.4 | 274              | 30.7 |
| Missing           | 0             |      | 1                |      |
| Income            |               |      |                  |      |
| <\$10,000         | 49            | 34.5 | 247              | 29.7 |
| \$10,000-19,999   | 45            | 31.7 | 222              | 26.7 |
| \$20,000-29,999   | 17            | 12.0 | 111              | 13.4 |
| \$30,000-49,999   | 13            | 9.2  | 102              | 12.3 |
| ≥\$50,000         | 18            | 12.7 | 149              | 17.9 |
| Missing           | 9             |      | 62               |      |

| <b>Table 3. Preliminary comparison of cases and controls for suspected breast cancer risk and protective factors in the South Texas Women's Health Project</b> |                      |       |                         |      |                                               |            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-------|-------------------------|------|-----------------------------------------------|------------|
| <b>Characteristic</b>                                                                                                                                          | <b>Cases (n=151)</b> |       | <b>Controls (n=893)</b> |      | <b>Adjusted for age and menopausal status</b> |            |
| Breast cancer among first-degree relatives                                                                                                                     |                      |       |                         |      |                                               |            |
| No                                                                                                                                                             | 132                  | 89.2  | 810                     | 92.7 | 1.0                                           | (referent) |
| Yes                                                                                                                                                            | 16                   | 10.8  | 64                      | 7.3  | 1.6                                           | (0.9-2.8)  |
| Missing                                                                                                                                                        | 3                    |       | 19                      |      |                                               |            |
| Mammograms                                                                                                                                                     |                      |       |                         |      |                                               |            |
| 0                                                                                                                                                              | 3                    | 2.0   | 2                       | 0.2  | 1.0                                           | (referent) |
| 1-2                                                                                                                                                            | 53                   | 35.6  | 172                     | 19.4 | 0.2                                           | (0.03-1.4) |
| ≥3                                                                                                                                                             | 93                   | 62.4  | 711                     | 80.3 | 0.1                                           | (0.01-0.1) |
| Missing                                                                                                                                                        | 2                    |       | 8                       |      |                                               |            |
| Diabetes                                                                                                                                                       |                      |       |                         |      |                                               |            |
| No                                                                                                                                                             | 106                  | 70.7  | 618                     | 69.4 | 1.0                                           | (referent) |
| Yes                                                                                                                                                            | 44                   | 29.3  | 273                     | 30.6 | 0.9                                           | (0.6-1.3)  |
| Missing                                                                                                                                                        | 1                    |       | 2                       |      |                                               |            |
| Body mass index (quartiles among controls)                                                                                                                     |                      |       |                         |      |                                               |            |
| 16.2-26.5                                                                                                                                                      | 26                   | 117.6 | 217                     | 24.8 | 1.0                                           | (referent) |
| 26.6-30.7                                                                                                                                                      | 40                   | 27.0  | 220                     | 25.1 | 1.5                                           | (0.9-2.5)  |
| 30.8-34.4                                                                                                                                                      | 40                   | 27.0  | 217                     | 24.8 | 1.4                                           | (0.8-2.5)  |
| 34.5-69.5                                                                                                                                                      | 42                   | 28.4  | 221                     | 25.3 | 1.5                                           | (0.9-2.6)  |
| Missing                                                                                                                                                        | 3                    |       | 18                      |      |                                               |            |
| Moderate physical activity (tertiles among controls)                                                                                                           |                      |       |                         |      |                                               |            |
| 0                                                                                                                                                              | 79                   | 53.0  | 424                     | 48.0 | 1.0                                           | (referent) |
| 0.1-2                                                                                                                                                          | 23                   | 15.4  | 155                     | 17.6 | 0.8                                           | (0.5-1.3)  |
| 2.1-60                                                                                                                                                         | 47                   | 31.5  | 304                     | 34.4 | 0.8                                           | (0.5-1.1)  |
| Missing                                                                                                                                                        | 2                    |       | 10                      |      |                                               |            |
| Phytoestrogen intake (quartiles among controls)                                                                                                                |                      |       |                         |      |                                               |            |
| 0-17.6                                                                                                                                                         | 27                   | 18.1  | 216                     | 24.9 | 1.0                                           | (referent) |
| 17.7-26.9                                                                                                                                                      | 37                   | 24.8  | 218                     | 25.1 | 1.3                                           | (0.8-2.2)  |
| 27.0-39.7                                                                                                                                                      | 46                   | 30.9  | 217                     | 25.0 | 1.5                                           | (0.9-2.6)  |
| 39.8-146.7                                                                                                                                                     | 39                   | 26.2  | 217                     | 25.0 | 1.4                                           | (0.8-2.3)  |
| Missing                                                                                                                                                        | 2                    |       | 25                      |      |                                               |            |

Preliminary results have shown an increased breast cancer risk with a positive family history of breast cancer, increasing body mass index, and increasing phytoestrogen intake (see Table 3). A decreased breast cancer risk was evident with increasing number of mammograms, and increasing hours per week of moderate physical activity. Although we had hypothesized

that insulin resistance would be positively associated with breast cancer, thus far we have found a slightly reduced breast cancer risk (OR 0.9, 95% CI 0.6-1.3) among women who report a positive history of Type 2 diabetes. These preliminary results attest to the quality of the data. We will fully complete investigation task 10 by performing final statistical analysis to test study hypotheses at the end of the study. We partially completed investigation task 11 by Dr. Sanderson (UTSPH) presenting on cancer registration at the Valley Baptist Medical Center-Harlingen Tumor Conference on November 20, 2006. We partially completed investigation task 12 by Dr. Sanderson (UTSPH) becoming principal investigator of a project funded by the National Center on Minority Health and Health Disparities to conduct a study of women diagnosed with high risk-human papillomavirus which places them at high risk of cervical cancer. We will partially complete, further complete or fully complete investigation tasks 13 through 15 in subsequent years. We partially completed investigation task 16 by Dr. Sanderson (UTSPH) and Dr. Nair (UTB) submitting a Synergistic Idea Award application to the Department of Defense to conduct a substudy of the South Texas Women's Health Project to investigate genes associated with obesity and diabetes.

Although our initial funding was for four years, Dr. Peltz (UTB) received a no cost extension to continue the project through August, 2008. During the fifth year of the project we will partially complete, further complete, or fully complete training tasks 2, 3, 7 and 8, and investigation tasks 1 through 16.

### **Key Research Accomplishments**

- Since receiving his MPH under training task 1, Dr. Peltz (UTB) published his master's thesis in Archives of Medical Research, and submitted abstracts from his leptin project funded by the University of Texas Health Science Center at San Antonio to two conferences.
- Further completed training task 2 by Dr. Sanderson (UTSPH) continuing to receive funding from the Texas Cancer Council to investigate the possibility of utilizing electronic pathology lab reporting to the Texas Cancer Registry on the Texas and Mexico sides of the border.
- Further completed training tasks 3, 7, and 8 by obtaining continuing institutional review board approval from several entities, and by revising the study design as needed. Dr. Sanderson (UTSPH) received additional funding to conduct a pilot study of the South Texas Women's Health Project. Dr. Peltz (UTB) received supplemental funding from the Department of Defense to add urinary excretion of phytoestrogen to the South Texas Women's Health Project.
- Partially completed investigation tasks 1 through 9 by recruiting breast cancer cases and controls; conducting in-person and telephone interviews; collecting anthropometric measurements and blood; abstracting medical records; processing and storing blood samples; completing enzyme-linked immunosorbent assays; completing high-performance liquid chromatography analysis; entering data for all questionnaires and assays; and performing interim statistical analysis.
- Partially completed investigation task 12 by Dr. Sanderson (UTSPH) becoming principal investigator of a project funded by the National Center on Minority Health and Health

Disparities to conduct a study of women diagnosed with high risk-human papillomavirus which places them at high risk of cervical cancer.

- Partially completed investigation task 16 by Dr. Sanderson (UTSPH) and Dr. Nair (UTB) submitted a Synergistic Idea Award application to the Department of Defense to conduct a substudy of the South Texas Women's Health Project to investigate genes associated with obesity and diabetes.

## Reportable Outcomes

### 1) Manuscripts

Coker AL, Sanderson M, Fadden MK. Psychosocial stress, coping and prostate cancer. *Ethnicity Dis* 2006;16:978-987.

Sanderson M, Coker AL, Perez A, Du XL, Peltz G, Fadden MK. A multilevel analysis of socioeconomic status and prostate cancer risk. *Ann Epidemiol* 2006;16:901-907.

Sanderson M, Daling JR, Malone KE, Doody DR. Perinatal factors and mortality from breast cancer. *Cancer Epidemiol Biomark Prev* 2006;15:1984-1987.

Meyer TE, Coker AL, Sanderson M, Symanski E. A case-control study of farming and prostate cancer in African American and Caucasian men. *Occup Environ Med* 2007;64:155-160.

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### 2) Abstracts

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Peltz G, Sanderson M, Cortez E, Calil R, Aguirre M. Comparative study between waist circumference and trunk fat mass using segmental bioelectrical impedance analysis. Annual Meeting of the North American Association for the Study of Obesity, New Orleans, LA, October, 2007.

Peltz G, Sanderson M, Wittenburg D, Bailey M, Aguirre K, Reyes-Chaves J, Aguirre MT, Calil R, Fadden MK. Body composition by bioelectrical impedance analysis and air-displacement plethysmography: a comparative study. Annual Meeting of the North American Association for the Study of Obesity, New Orleans, LA, October, 2007.

### 3) Grants

|                    |                                                                                                                                                  |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
| Name:              | Insulin Resistance and Breast Cancer (Sanderson, PI)                                                                                             |
| Funding Agency:    | National Institute on Minority Health and Health Disparities                                                                                     |
| Period of Funding: | March 1, 2003 – February 28, 2005                                                                                                                |
| Amount:            | \$84,000 (total direct)                                                                                                                          |
|                    |                                                                                                                                                  |
| Name:              | Cancer Disparities, Reporting and Prevention among Texas-Mexico Border Hispanics (Sanderson, PI)                                                 |
| Funding Agency:    | National Institute on Minority Health and Health Disparities                                                                                     |
| Period of Funding: | March 1, 2003 – February 28, 2008                                                                                                                |
| Amount:            | \$547,645 (total direct)                                                                                                                         |
|                    |                                                                                                                                                  |
| Name:              | Serum Leptin Values in Mexican Americans: Association with Body Fat, Body Mass Index, and Obesity (Peltz, PI)                                    |
| Funding Agency:    | University of Texas Health Science Center at San Antonio                                                                                         |
| Period of Funding: | September 1, 2004 – August 31, 2005                                                                                                              |
| Amount:            | \$39,614 (total direct)                                                                                                                          |
|                    |                                                                                                                                                  |
| Name:              | Partnership between the Texas Cancer Registry and the UTSPH-B for Assuring Timely, Complete and Accurate Cancer Data in the LRGV (Sanderson, PI) |
| Funding Agency:    | Texas Cancer Council                                                                                                                             |
| Period of Funding: | March 1, 2005 – August 31, 2006                                                                                                                  |
| Amount:            | \$146,011 (total direct)                                                                                                                         |
|                    |                                                                                                                                                  |
| Name:              | Supplement - Interrelationships of Hormones, Diet, Body Size, and Breast Cancer Among Hispanic Women (Peltz, PI)                                 |
| Funding Agency:    | Department of Defense                                                                                                                            |
| Period of Funding: | August 8, 2005 – August 31, 2007                                                                                                                 |
| Amount:            | \$79,161 (total direct)                                                                                                                          |

### **Conclusions**

The overall goal of this Minority Institution Partnership Training Award is to further strengthen the collaborative relationship between the minority institution, UTB, and the collaborating institution, UTSPH. The UTSPH established a regional campus on the UTB campus in 2001, and the Co-Principal Investigator of the partnership from UTSPH is located in Brownsville. The vision of UTB and the UTSPH, Brownsville regional campus is to conduct community-based participatory research in areas deemed important by the community.

The training program will focus on breast cancer etiology, specifically the interrelationships between hormones, diet, body size and breast cancer among Hispanic women. The Lower Rio Grande Valley (LRGV) of Texas is an exceptional location to perform breast cancer research because 85 percent of the population is Hispanic. Hispanic women in the LRGV have a relatively low incidence of breast cancer compared with non-Hispanic white women. In comparison with Hispanic women in the US, Hispanic women residing in the LRGV have a higher

mortality from breast cancer. In contrast, Hispanic women are at greater risk of insulin resistance. This research will allow us to investigate whether the reduced risk of breast cancer among Hispanic women in the LRGV may be related to their higher genetic susceptibility to insulin resistance. Women tend to develop insulin resistance if they are genetically susceptible, gain excess weight due to physical inactivity, and consume a high-fat, low-fiber diet during adolescence and adulthood. It is clear that this area of research has promise with regard to explaining the different breast cancer incidence and mortality rates by ethnicity. We hypothesize that the South Texas Women's Health Project conducted as part of the training program will be useful in identifying factors associated with decreased breast cancer risk among Hispanic women.

While faculty from UTSPH have expertise in breast cancer research, faculty from UTB have strong ties with the medical and lay community in Brownsville and Cameron County. To date, no breast cancer research has been conducted in Cameron County. By partnering together, these institutions hope to achieve the following goals: 1) develop a regional cancer registry, 2) build infrastructure to conduct population-based case-control studies of breast cancer, 3) initiate studies to investigate factors which may protect Hispanic women from breast cancer, and 4) establish an outstanding breast cancer research program.

## References

Coker AL, Sanderson M, Fadden MK. Psychosocial stress, coping and prostate cancer. *Ethnicity Dis* 2006;16:978-987.

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Peltz G, Sanderson M, Perez A, Sexton K, Caceres D, Fadden MK. Serum leptin concentration, adiposity, and body fat distribution in Mexican Americans: A cross-sectional study. *Arch Med Res* 2007;563-570.

## **Statement of Work**

### **Interrelationships of Hormones, Diet, Body Size and Breast Cancer among Hispanic Women**

#### Phase 1: Training phase (Year 1)

- 1) Complete coursework toward Master's of Public Health degree
- 2) Liaise with local medical providers, health clinics and state health agencies to encourage reporting of breast cancer to the Texas Cancer Registry
- 3) Identify sites for data collection with local health providers and health clinics
- 4) After consultation with local health providers design a case-control study to include completion of a questionnaire, urine collection, anthropometry and a blood draw
- 5) Develop a questionnaire appropriate for use with the local Hispanic population
- 6) Design protocols for data collection, laboratory work, tracking system, data entry programs, and write manual of operations
- 7) Initiate institutional review board approval through local and federal channels
- 8) Pilot test study methods and revise the study design as needed

#### Phase 2: Investigation Phase (Years 2 through 4)

- 1) Identify and recruit 500 breast cancer cases and 1000 controls identified by mammography centers
- 2) Complete questionnaires to obtain information on breast cancer risk factors, personal health history (e.g., type 2 diabetes), medication history (e.g., estrogen and insulin), and diet
- 3) Collect anthropometric measurements and pre-diagnostic blood
- 4) Abstract medical records for relevant health history and pathology data
- 5) Process and store blood samples
- 6) Complete enzyme-linked immunosorbent assays for insulin, insulin-like growth factor-I, insulin-like growth factor binding protein-3, and sex hormone-binding globulin, enzyme immunoassays for estradiol and estrone, and measure glucose on a biochemistry analyzer
- 7) Complete high-performance liquid chromatography (HPLC) analysis for urinary phytoestrogens
- 8) Complete data entry of all questionnaires and assays
- 9) Perform interim statistical analyses at end of year 2 to assess data quality
- 10) Perform final statistical analyses to test study hypotheses
- 11) Consult with local health providers and health clinics regarding the cancer reporting mechanism and provide training as needed
- 12) Expand data collection to cancers other than breast cancer as a means of developing a regional Lower Rio Grande Valley cancer registry.
- 13) Disseminate findings to the Texas Department of Health, the Department of Defense, and local health providers and health clinics
- 14) Prepare manuscripts to report study results
- 15) Archive dataset for future analyses and future patient follow-up
- 16) Submit proposals to conduct larger population-based case-control studies of breast cancer in the Lower Rio Grande Valley

# STRESS, COPING, SOCIAL SUPPORT, AND PROSTATE CANCER RISK AMONG OLDER AFRICAN AMERICAN AND CAUCASIAN MEN

**Objectives:** While psychosocial stress and high effort coping have been associated with reduced immune function, no epidemiologic study has addressed psychological stress and risk of prostate cancer. The purpose of this analysis was to investigate the association between stress, coping, social support, and risk of prostate cancer among older men (age 65–79 years).

**Design:** Population-based case-control study in South Carolina.

**Participants:** Cases were 400 incident, histologically confirmed prostate cancer cases identified through the South Carolina Central Cancer Registry between 1999 and 2001 (70.6% response rate). Controls were 385 men identified through the 1999 Health Care Financing Administration Medicare beneficiary file for South Carolina (63.8% response rate).

**Main Outcome Measures:** Consenting participants completed telephone interviews addressing demographics (age, race, income, education, marital status, body mass index), medical and prostate cancer screening history, stress (Global Perceived Stress), coping (John Henryism Scale), and social support.

**Results:** After adjusting for age, race, and South Carolina region, higher John Henryism scores (>24) were modestly associated with prostate cancer risk relative to lower scores (<24) (adjusted odds ratio 1.63, 95% confidence interval 1.11–2.40). This effect is somewhat more pronounced among those perceiving some stress, yet the effect of John Henryism on prostate cancer risk was reduced among those with high levels of social support. Neither higher stress nor social support alone was associated with prostate cancer risk.

**Conclusions:** Higher John Henryism scores indicating high-effort coping may be associated with an increase in prostate cancer risk. (*Ethn Dis.* 2006;16:978–987)

**Key Words:** Coping, Epidemiology, Prostate Neoplasms, Psychological Stress, Race

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Ann L. Coker, PhD; Maureen Sanderson, PhD; Gary L. Ellison, PhD; Mary K. Fadden, MPH

## INTRODUCTION

Most studies addressing the effect of chronic stress on health find that chronic stress is associated with an increased risk of infectious diseases<sup>1–7</sup> including HIV,<sup>8,9</sup> cardiovascular disease,<sup>10–14</sup> and cancer.<sup>15–17</sup> Hilakivi-Clark and Dickson<sup>16</sup> found that male transgenic mice overexpressing transforming growth factor- $\alpha$  (TGF- $\alpha$ ) who lived in stressful environments with aggressive non-siblings developed hepatocellular tumors earlier and had greater tumor burden than did mice housed in less stressful environments. Ben-Eliyahu et al<sup>17</sup> found that stress-induced suppression of natural killer cell activity (NKA) was sufficient to cause enhanced tumor development. Byrnes et al<sup>18</sup> proposed a causal model for the association between stress, depression, and cancer. Stress and depression are associated with a deregulation of inflammatory cytokines; stress is associated with increased expression of interleukin (IL)-1 $\beta$  and down-regulation of IL-2, interferon (IFN)- $\gamma$  (Interferon), NKA, and major histocompatibility complex (MHC) class II molecules.<sup>19</sup> Stress and depression can foster tumor progression by inhibiting expression of MHC class I and II molecules and through NKA reduction. Although several recent studies

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have identified the negative effect of chronic stress on health,<sup>1,20</sup> we found no published epidemiologic studies that have addressed psychological stress and risk of prostate cancer development. Epidemiologic studies have investigated psychological stress predominately by using stressful life events measures and cancers of the cervix,<sup>21,22</sup> lung,<sup>23</sup> breast,<sup>24–30</sup> and colon.<sup>31–34</sup>

Coping characteristics of the individual and social support from family and friends can modify the association between stress and disease. Among caregivers, Esterling et al<sup>35</sup> found evidence that social support may modulate the effect of chronic stress on immune function. Social support may be a key moderator of the effect of psychosocial stress on cancer development. In a meta-analysis, Suls and Fletcher<sup>36</sup> found that coping style (cognitive avoidance vs attentive-confrontive) was more favorably associated with acute stress; however, information-seeking was associated with better long-term adjustment to stress. James et al<sup>37,38</sup> developed the construct of John Henryism as a measure

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of high-effort active coping, defined as an individual's self-perception that environmental and psychosocial demands can be met through hard work and determination. Prolonged high-effort coping with chronic psychosocial stressors may result in adverse health effects, particularly for those with limited social or economic resources<sup>39</sup> who, in the United States, may be disproportionately African American. James et al<sup>37</sup> found that higher John Henryism Scale (JHS) scores were associated with hypertension among low-income African Americans. In a recent review, Bennett et al<sup>39</sup> reported that 9 of 16 studies evaluating John Henryism and hypertension found an association; many of these positive studies reported interactions between John Henryism, lower socioeconomic status, and stress. Like hypertension, prostate cancer is a chronic disease that African Americans are significantly more likely than Whites to experience. The high-effort coping that contributes to the racial difference in blood pressure may be relevant to the racial disparity in prostate cancer incidence.

Ellison et al<sup>40</sup> proposed a conceptual model for the role of stress, coping, and social support on prostate cancer development; this model was adapted from the work of Adler and Matthews.<sup>41</sup> Ellison's model hypothesizes that psychological stress may lead to prostate cancer through physiologic responses to environmental stressors.<sup>40</sup> The physiologic response to environmental stress is a function of the individual's perception of the stress and his ability to cope with the stress. Those who perceive life stressors as threatening and lack effective coping strategies and resources to address these environmental stressors may be at greater risk of cancer because of their inability to mount an effective immunologic response to carcinogenesis.<sup>40</sup>

The purpose of this analysis was to investigate whether higher perceived stress, high-effort coping, and lower social support may interact to increase

the risk of prostate cancer among African American and Caucasian men in a population-based case-control study.

## METHODS

### Cases and Controls

Details of this population-based case-control study have been reported elsewhere.<sup>42</sup> Briefly, patients aged 65–79 years who were diagnosed with primary, invasive, histologically confirmed prostate cancer between October 1999 and September 2001 were identified through the South Carolina Central Cancer Registry (SCCCR). During the study period, 551 Caucasian men and 245 African American men with localized disease (stages I and II) and 98 Caucasian men and 70 African American men with advanced disease (stages III and IV) who met the eligibility criteria were reported to the SCCCR. All eligible cases with advanced disease and a random sample of men with localized disease within five-year age groups (42% of Caucasian cases and 83% of African American cases) were selected. A total of 426 prostate cancer cases (70.6% of eligible cases) completed a standardized telephone interview. Of potentially eligible cases, 90 physicians refused (13.0%), 71 patients refused (10.3%), 24 died before the interview (3.5%), 59 were not located (8.5%), and 23 were too sick to participate (3.3%). After eliminating seven prevalent prostate cancer patients and 19 patients who did not provide complete interview data, 400 cases remained for analyses.

Control subjects were South Carolina residents aged 65–79 who were randomly sampled from the 1999 Health Care Financing Administration (HCFA) Medicare beneficiary file. Controls were frequency matched to cases on age (five-year age groups), race (Caucasian, African American), and geographic region (western, middle, and eastern third of the state). A total

of 482 control subjects (63.8%) completed the interview. Of potentially eligible controls, 108 refused (14.3%), 22 died before the interview (2.9%), 112 were not located (14.8%), and 32 were too sick to participate (4.2%). After eliminating 52 controls with prevalent prostate cancer and 45 controls whose interviews were incomplete, 385 controls remained for analyses.

Cases and controls were recruited through mailings that described the study and informed the potential participant that an interviewer would contact them. Since the HCFA file does not contain telephone numbers, controls whose phone numbers could not be located through directory assistance, telephone directories, or reverse directories were sent an additional letter asking for a preferred contact number. Trained interviewers from the University of South Carolina Survey Research Laboratory conducted computer-assisted telephone interviews with subjects who provided verbal consent with the understanding that written consent would be obtained. Telephone interviews of 30–40 minutes in length collected information on demographic characteristics, socioeconomic status, alcohol and tobacco use, and medical history (including diabetes, stroke, myocardial infarction, cirrhosis or other liver disease, hypertension and hypercholesterolemia, and family history of cancer). Most exposures pertained to the period before a reference date: the date of diagnosis for cases and an assigned date for controls. For psychosocial factors, this time frame was the one-year period before the diagnosis or reference date. Institutional review boards of the University of South Carolina, the Centers for Disease Control and Prevention, and the National Cancer Institute approved this project's data collection procedures.

### Stress, Coping, and Social Support Measurement

We used seven items from the 10-item Global Perceived Stress (GPS)<sup>43</sup>

scale as a measure of self-perceived stress. Respondents were asked to think about how they usually felt before the reference date. Response options were as follows: never (1), almost never (2), sometimes (3), fairly often (4), and very often (5). When assessing the psychometric properties of the scale, we identified two factors within this scale. Factor I, which generally measures stress (hereafter, perceived stress), included the following three items: How often: 1) did you feel nervous and stressed (correlation within the factor=.76); 2) were you angered because of things that happened that were outside your control (correlation=.75); and 3) did you feel difficulties were piling up so high that you could not overcome them (correlation=.68). Factor II generally measured perceived ability to cope or control life stressors (hereafter, control stress) and included the following four items: How often: 1) did you feel that you were effectively coping with important changes that were occurring in your life (correlation=.50); 2) did you feel confident about your ability to handle your personal problems (correlation=.75); 3) were you able to control irritations in your life (correlation=.72); and 4) did you feel that you were on top of things (correlation=.72). The four items in the control stress subscale were reverse coded such that a higher score indicated less perceived control over stress. The higher the total GPS score, the greater the perceived stress and the lower the perceived control over stress. Cronbach alpha  $\alpha$  for our 7-item scale was .50, which indicates limited internal consistency of the scale, yet the alphas for the perceived stress (.60) and control stress (.61) subscales were higher than the alpha for the GPS scale. We created cut-points based on the distribution in the controls to indicate three levels of the continuous scores. The highest category includes those answering most items as sometimes to fairly often (scores >20), the intermediate category includes those who answered questions in general as

almost never to sometimes (scores 14–20), and the lowest category includes those answering the seven items as generally never to almost never (scores 7–13).

We used a shortened version of the 12-item JHS as a measure of high-effort coping.<sup>37</sup> This 12-item scale includes three main themes: efficacious mental and physical vigor, a strong commitment to hard work, and a single-minded determination to succeed. We included two of the four items for each theme to create our reduced six-item scale. Respondents were instructed to think about how they saw themselves as a person living and doing things in the real world before the referent date. The five response options for each statement ranged from strongly agree (5) to strongly disagree (1). Higher scores indicated higher effort coping. The following six items were used: "I always felt I could make my life pretty much what I wanted to make of it"; "Once I made up my mind to do something I stayed with it until the job was completely done"; "When things didn't go the way I wanted them to, that just made me work even harder"; "Sometimes I felt that if anything was going to be done right, I had to do it myself"; "I didn't let my personal feelings get in the way of doing a job"; and "Hard work really helped me to get ahead in life." The Cronbach's alpha for this six-item scale, ranging from 6–30, was .64, similar to the .67 reported by James et al.<sup>37</sup> Note that the JHS does not assess coping in response to stress but is a generalized approach to one's work life. Cut-points were created to reflect meaningful differences in scores. The highest group included those who consistently answered strongly agree on almost all items (scores 29–30), intermediates included those answering agree to strongly agree on most items (scores 25–28), and the lowest category included those answering strongly disagree to agree on some items (scores 6–24).

We used three items based on the measure developed by Sarason et al to

assess social support.<sup>44</sup> Again, respondents were instructed to think about their social networks before the referent date. The following three items were used to measure social support: "There was someone: 1) who accepted me totally including both my worst and best points; 2) I could count on to care about me, regardless of what was happening to me; and 3) I could count on to help me feel better when I was feeling down in the dumps." Five response options ranged from strongly agree (5) to strongly disagree (1). Higher scores indicated greater perceived support; scores ranged from 3 to 15 with a Cronbach's alpha coefficient of .68. Again, because this scale was skewed toward the majority who reported high social support, we created cut-points to reflect meaningful comparisons. The highest cut-point included those who answered all items as strongly agree (scores=15), the intermediate included those answering agree to strongly agree (scores 13–14), and the lowest category included those answering strongly disagree to agree (scores 3–11).

## STATISTICS

We used unconditional logistic regression to estimate the relative risk of prostate cancer associated with 1) high stress, 2) high-effort coping, and 3) social support, while controlling for potential confounding factors.<sup>45</sup> Potential confounding factors included age, race, educational level, marital status, family history of prostate cancer, body mass index, alcohol and tobacco use, and number of prostate cancer screenings (digital rectal exam [DRE] or prostate-specific antigen [PSA] test) in the five years before the reference date. Since screening by DRE and PSA test were highly correlated ( $r=.61$ ,  $P<.0001$ ), we created a variable to combine the number of prostate cancer screenings in the past five years by DRE or PSA test. Most studies addressing John Henryism have performed analyses by race; there-

fore, we followed this pattern in Tables 2–4. Body mass index, defined as self-reported weight (kg) before reference date divided by the square of self-reported height ( $m^2$ ), was categorized as normal weight ( $<25.0 \text{ kg}/m^2$ ), overweight ( $25.0\text{--}29.9 \text{ kg}/m^2$ ), or obese ( $\geq 30.0 \text{ kg}/m^2$ ). Dummy variables based on the cut-points for each measure were included in the logistic regression model. Odds ratios (ORs) for psychological factors and prostate cancer are presented by race and adjusted for age and South Carolina region. No other confounding factors materially affected the ORs for stress, coping, or social support and prostate cancer.

## RESULTS

The final sample included 400 prostate cancer patients (160 African American and 240 Caucasian men) and 385 controls (161 African American and 224 Caucasian men). Crude ORs and 95% confidence intervals (CIs) for prostate cancer were presented for the risk factors of interest. Because of frequency matching, cases and controls were, in general, comparable in age and race. Having had benign prostatic hyperplasia (BPH) or a family history of prostate cancer was associated with incident prostate cancer (data not presented). Annual PSA tests or DREs over the past five years before the referent date were also associated with prostate cancer ( $P$  value for trend  $<.0001$ ). No other risk factors were associated with prostate cancer risk in these data.

Table 1 presents the mean scores with standard deviations for GPS, JHS, and social support by levels of risk factors among controls. Factors associated with having higher stress scores included African American race, less education, and lower income. Higher John Henryism scores were observed among African American men and those with less education, yet these differences were not statistically significant. Lastly, the following factors were associated with

higher social support scores: Caucasian race, higher education, higher income, being married or living as married, and having annual prostate cancer screening.

Presented in Table 2 are the multivariate ORs for categories of each stress, coping, and social support scale (full GPS scale, perceived stress subscale, ability to control stress subscale, JHS, and social support scales) for cases and controls. Neither the full GPS measure nor the ability to control stress subscale were associated with prostate cancer. The perceived stress subscale may be associated with prostate cancer risk among African American men; however, the association does not follow a dose-dependent pattern. Higher John Henryism scores may be associated with prostate cancer risk, yet again the pattern did not reflect a dose-dependent pattern. The association was only statistically significant for African American men when comparing intermediate-to-low JH scores. Statistically nonsignificant ORs in the same direction were observed for all the other race-specific associations with John Henryism. Social support was not associated with prostate cancer risk. No evidence of interaction was found with the Breslow-Day test for homogeneity of the odds ratios for prostate cancer risk and psychosocial measures across race; therefore, subsequent analysis will include both race groups in one model.

We also addressed the potential for variables to interact with stress (Table 3) and coping (Table 4) to modify prostate cancer risk. These factors include prostate cancer stage, social support, stress, occupation, education, race, and income. We conducted these subanalyses to be consistent with the conceptual model proposed by Ellison,<sup>40</sup> which suggests that men who experience stress, but are high-effort coping either because of coping styles or social or economic support, are at the greatest risk of cancer.

Table 3 addresses the association between stress scores (as two dummy

variables and a comparison of high and middle with low scores) and prostate cancer risk while adjusting for potentially modifying factors. In general, higher perceived stress scores were not consistently associated with prostate cancer risk in any subgroup investigated.

Table 4 presents the parallel analysis to that presented in Table 3. Higher and intermediate levels of JHS scores relative to lower scores were associated with an increased prostate cancer risk (OR 1.63, 95% CI 1.11–2.40). This association was similar among African American and Caucasian men. The effect of higher JHS scores on prostate cancer risk was somewhat more pronounced when perceived stress was intermediate or high. The effect of John Henryism on prostate cancer appears to be reduced among those with high social support. Neither education nor income modified the association between John Henryism and prostate cancer.

## DISCUSSION

These results provide limited support for the hypothesis presented by Ellison et al<sup>40</sup> that high-effort coping, as measured by the JHS, may be associated with a modest increase in risk of prostate cancer, particularly among those with lower social support. No racial differences in the effect of John Henryism on prostate cancer risk were noted. Neither social support nor higher perceived stress was associated with an increased prostate cancer risk.

The literature addressing psychological stress and breast cancer is perhaps most relevant to interpreting first study of stress and prostate cancer, since breast cancer is epidemiologically similar to prostate cancer.<sup>46</sup> Results from several recent cohort studies addressing perceived stress or stressful events and risk of subsequent breast cancer development are mixed. Of nine studies with at least five years of followup before breast cancer development, five found an

association with perceived stress or stressful events<sup>27-29,47,48</sup> while four did not.<sup>49-52</sup> We did not find that perceived stress was associated with prostate cancer risk. Since most studies that found an association between stress and breast cancer used stressful life events as a measure of stress, future studies assessing prostate cancer risk may also opt to measure stressful life events as well as perceived stress. No studies addressing John Henryism and breast cancer risk have been conducted.

As noted by Ellison et al,<sup>40</sup> chronic stress may affect prostate cancer risk. In response to stress, corticosteroid hormones, which have immunosuppressive properties,<sup>53</sup> including lower natural killer cell cytotoxicity,<sup>17</sup> are released. Prolonged stress may impair immune function, which may increase risk of carcinogenesis. In contrast to prior studies with other adverse outcomes,<sup>54</sup> we did not find that chronic perceived stress, unmitigated by high-effort coping or social support, increased the risk of prostate cancer.

South Carolina has one of the highest incidence rates of prostate cancer,<sup>55</sup> and African American men are at significantly greater risk than their Caucasian counterparts.<sup>56</sup> In this study, African American men had higher perceived stress, higher John Henryism, and lower social support scores than did Caucasian men. African American men are well known to have higher prostate cancer rates than do Caucasians. This study adds to the literature as the first study to address perceived stress, coping, social support, and prostate cancer among both African American and Caucasian men in a region with high prostate cancer rates.

Our study has several limitations to consider in interpreting these results. While we attempted to frame the subject's recall of stress, coping, and social support to experiences before prostate cancer development (eg, before the referent date), patients may have difficulty recalling feelings and experi-

**Table 1. Comparison of controls (N=385) on stress, coping, and social support scores**

| Risk Factor                              | Global Perceived Stress Score | John Henryism (Coping) Score | Social Support Score |
|------------------------------------------|-------------------------------|------------------------------|----------------------|
|                                          | (Mean $\pm$ SD)               | Mean ( $\pm$ SD)             | (Mean $\pm$ SD)      |
| Age (years)*                             |                               |                              |                      |
| 65-69 (n=169)                            | 14.88 (3.70)                  | 27.10 (3.12)                 | 13.70 (2.14)         |
| 70-74 (n=112)                            | 15.29 (4.17)                  | 27.06 (3.43)                 | 13.77 (2.00)         |
| 75-79 (n=104)                            | 15.40 (4.34)                  | 27.54 (2.81)                 | 13.62 (2.11)         |
| P value for trend                        | .27                           | .32                          | .78                  |
| Race†                                    |                               |                              |                      |
| African American (n=161)                 | 15.88 (4.71)‡                 | 27.46 (3.37)                 | 13.30 (2.41)‡        |
| Caucasian (n=224)                        | 14.61 (3.35)                  | 27.02 (2.95)                 | 13.98 (1.77)         |
| Education†                               |                               |                              |                      |
| Less than high school graduate (n=142)   | 16.36 (4.63)                  | 27.60 (3.29)                 | 13.31 (2.40)         |
| High school graduate (n=90)              | 15.19 (3.75)                  | 27.09 (3.44)                 | 13.81 (2.00)         |
| Some college or technical school (n=153) | 13.98 (3.15)                  | 26.89 (2.75)                 | 14.01 (1.74)         |
| P value for trend                        | <.0001                        | .06                          | .004                 |
| Annual income                            |                               |                              |                      |
| <\$20,000 (n=104)                        | 16.63 (4.43)                  | 27.30 (3.45)                 | 13.32 (2.24)         |
| \$20,000-\$29,999 (n=57)                 | 15.46 (3.74)                  | 27.33 (2.67)                 | 13.84 (1.64)         |
| \$30,000-\$39,999 (n=54)                 | 14.87 (3.20)                  | 27.33 (2.95)                 | 13.85 (1.74)         |
| \$40,000-\$49,999 (n=36)                 | 13.61 (3.54)                  | 27.63 (2.97)                 | 13.86 (1.96)         |
| ≥\$50,000 (n=77)                         | 13.51 (2.55)                  | 27.08 (2.68)                 | 14.25 (1.76)         |
| Missing (n=57)                           |                               |                              |                      |
| P value for trend                        | <.0001                        | .77                          | .002                 |
| Marital status                           |                               |                              |                      |
| Single§ (n=77)                           | 15.83 (4.38)                  | 27.36 (3.07)                 | 13.29 (2.46)         |
| Married   (n=308)                        | 14.93 (3.86)                  | 27.21 (3.06)                 | 13.83 (1.92)¶        |
| Body mass index (mg/kg <sup>2</sup> )    |                               |                              |                      |
| ≤24.9, normal weight (n=111)             | 15.17 (3.68)                  | 27.81 (2.68)                 | 13.82 (2.00)         |
| 25.0-29.9, overweight (n=173)            | 14.91 (3.80)                  | 27.01 (3.10)                 | 13.82 (1.77)         |
| ≥30.0, obese (n=94)                      | 15.32 (4.65)                  | 26.97 (3.32)                 | 13.54 (2.42)         |
| P value for trend                        | .84                           | .05                          | .36                  |
| History of benign prostatic hyperplasia  |                               |                              |                      |
| No (n=280)                               | 15.00 (4.15)                  | 27.35 (3.07)                 | 13.70 (2.10)         |
| Yes (n=105)                              | 15.40 (3.52)                  | 26.87 (3.25)                 | 13.66 (2.07)         |
| Family history of prostate cancer        |                               |                              |                      |
| No (n=325)                               | 15.21 (4.04)                  | 27.19 (3.18)                 | 13.65 (2.12)         |
| Yes (n=60)                               | 14.70 (3.85)                  | 27.20 (2.94)                 | 13.97 (1.90)         |
| History of hypertension                  |                               |                              |                      |
| No (n=182)                               | 15.27 (4.04)                  | 27.27 (3.07)                 | 13.81 (1.96)         |
| Yes (n=203)                              | 14.99 (4.00)                  | 27.11 (3.22)                 | 13.61 (2.19)         |
| Annual prostate cancer screening#        |                               |                              |                      |
| No (n=206)                               | 15.46 (4.19)                  | 25.75 (2.84)                 | 13.49 (2.26)         |
| Yes (n=169)                              | 14.71 (3.78)                  | 27.25 (2.87)                 | 13.99 (1.77)¶        |
| Ever drank alcohol                       |                               |                              |                      |
| No (n=109)                               | 14.92 (4.11)                  | 27.56 (3.33)                 | 13.69 (2.11)         |
| Yes (n=276)                              | 15.20 (3.98)                  | 27.08 (3.04)                 | 13.71 (2.08)         |
| Cigarette smoking history                |                               |                              |                      |
| Never smoker (n=118)                     | 14.85 (4.31)                  | 27.06 (3.49)                 | 13.86 (2.20)         |
| Former smoker (n=204)                    | 15.07 (3.83)                  | 27.25 (3.05)                 | 13.75 (1.96)         |
| Current smoker (n=63)                    | 15.74 (4.03)                  | 27.23 (2.77)                 | 13.60 (2.28)         |

Table 1. Continued

| Risk Factor                                                                        | Global Perceived Stress Score | John Henryism (Coping) Score | Social Support Score |
|------------------------------------------------------------------------------------|-------------------------------|------------------------------|----------------------|
|                                                                                    | (Mean $\pm$ SD)               | Mean ( $\pm$ SD)             | (Mean $\pm$ SD)      |
| <i>P</i> value for trend                                                           | .19                           | .67                          | .89                  |
| SD=standard deviation                                                              |                               |                              |                      |
| * Adjusted for South Carolina region (three areas).                                |                               |                              |                      |
| † Adjusted for age (categorical variable), South Carolina region (three areas).    |                               |                              |                      |
| ‡ $P < .01$ .                                                                      |                               |                              |                      |
| § Single includes single, never married, divorced, separated, widowed.             |                               |                              |                      |
| Married includes currently married and living as married.                          |                               |                              |                      |
| ¶ $P = .01-.05$ .                                                                  |                               |                              |                      |
| # Annual digital rectal exam or PSA screening received during the past five years. |                               |                              |                      |

ences before a prostate diagnosis. Thus, the measure of stress, coping, and social support among cases may be biased to reflect: 1) feelings that are a consequence of prostate cancer, or 2) feelings that did not change with prostate cancer diagnosis. Relative to controls, cases may have recalled social support after diagnosis. The measures of stress and coping are generalized measures of behaviors that are less likely to be affected by a specific recent health threat and, therefore, less likely to be mis-

Table 2. Odds ratios for prostate cancer and stress, coping, and social support among men aged 65–79 by race

|                                             | African American Men ( <i>n</i> =321) |                       |                       | Caucasian Men ( <i>n</i> =464) |                       |                       |
|---------------------------------------------|---------------------------------------|-----------------------|-----------------------|--------------------------------|-----------------------|-----------------------|
|                                             | Case <i>n</i> =160                    | Control <i>n</i> =161 | Adjusted* OR (95% CI) | Case <i>n</i> =240             | Control <i>n</i> =224 | Adjusted* OR (95% CI) |
| Full global perceived stress scale (GPS)†   |                                       |                       |                       |                                |                       |                       |
| High (GPS score >20)                        | 21 (13.3%)                            | 28 (17.8%)            | 1.18 (.47–2.63)       | 14 (5.9%)                      | 10 (4.5%)             | .85 (.43–1.68)        |
| Intermediate (GPS score 14–20)              | 88 (55.7%)                            | 74 (46.8%)            | .76 (.52–1.12)        | 123 (51.4%)                    | 129 (53.5%)           | 1.33 (.81–2.18)       |
| Low (GPS score 7–13)                        | 49 (31.0%)                            | 56 (35.4%)            | 1.00 REF              | 102 (42.7%)                    | 82 (34.0%)            | 1.00 REF              |
| <i>P</i> value for trend                    |                                       |                       | .53                   |                                |                       | .41                   |
| Missing                                     | 2                                     | 3                     |                       | 1                              | 3                     |                       |
| Perceived stress subscale (of GPS)          |                                       |                       |                       |                                |                       |                       |
| Higher (score 9–15)                         | 60 (37.7%)                            | 56 (34.8%)            | 1.40 (.85–2.31)       | 75 (31.3%)                     | 80 (35.7%)            | .67 (.43–1.06)        |
| Intermediate (score 7–8)                    | 38 (23.9%)                            | 27 (16.8%)            | 1.80 (.99–3.28)       | 79 (32.9%)                     | 80 (35.7%)            | .71 (.46–1.12)        |
| Lower (score 3–6)                           | 61 (38.4%)                            | 78 (48.5%)            | 1.00 REF              | 85 (35.8%)                     | 64 (28.6%)            | 1.00 REF              |
|                                             |                                       |                       | .17                   |                                |                       | .09                   |
| Ability to control stress subscale (of GPS) |                                       |                       |                       |                                |                       |                       |
| Higher (score >10)                          | 54 (34.0%)                            | 59 (37.3%)            | .80 (.47–1.38)        | 30 (12.5%)                     | 32 (14.5%)            | .88 (.50–1.55)        |
| Intermediate (score 7–9)                    | 51 (32.0%)                            | 51 (32.3%)            | .85 (.49–1.48)        | 95 (39.8%)                     | 85 (38.5%)            | 1.02 (.68–1.51)       |
| Lower (scores 4–6)                          | 54 (34.0%)                            | 48 (30.4%)            | 1.00 REF              | 114 (47.7%)                    | 104 (47.1%)           | 1.00 REF              |
|                                             |                                       |                       | .43                   |                                |                       | .74                   |
| Active coping (John Henryism (JH))‡         |                                       |                       |                       |                                |                       |                       |
| High (JH score 29–30)                       | 83 (52.5%)                            | 86 (53.4%)            | 1.69 (.86–3.30)       | 98 (41.4%)                     | 90 (40.5%)            | 1.44 (.85–2.44)       |
| Intermediate (JH score 25–28)               | 58 (36.7%)                            | 46 (28.6%)            | 2.19 (1.07–4.48)      | 104 (43.9%)                    | 85 (38.3%)            | 1.61 (.52–1.36)       |
| Low (JH score 12–24)                        | 17 (10.8%)                            | 29 (18.0%)            | 1.00 REF              | 35 (14.8%)                     | 47 (21.2%)            | 1.00 REF              |
| <i>P</i> value for trend                    |                                       |                       | .40                   |                                |                       | .31                   |
| Missing                                     | 3                                     | 0                     |                       | 3                              | 2                     |                       |
| Social support (SS)§                        |                                       |                       |                       |                                |                       |                       |
| High (SS score: 15)                         | 89 (56.3%)                            | 75 (46.2%)            | 1.30 (.96, 1.76)      | 156 (65.7%)                    | 131 (58.8%)           | 1.27 (.94, 1.73)      |
| Intermediate (SS score 12–14)               | 49 (16.5%)                            | 58 (17.7%)            | .87 (.66, 1.15)       | 69 (15.1%)                     | 75 (17.2%)            | .87 (.69, 1.10)       |
| Low (SS score 3–11)                         | 20 (27.2%)                            | 28 (36.1%)            | 1.00 REF              | 12 (19.2%)                     | 16 (24.0%)            | 1.00 REF              |
| <i>P</i> value for trend                    |                                       |                       | .09                   |                                |                       | .12                   |
| Missing                                     | 2                                     | 3                     |                       | 3                              | 2                     |                       |

OR= odds ratio; CI= confidence interval.

\* Adjusted for age (categorical variable), South Carolina region (three areas).

† Global Perceived Stress Scale: 7 items, range 7–29, Cronbach's alpha=.51.

‡ John Henryism Scale: 6 items, range 10 to 30, Cronbach's alpha=.66.

§ Social Support: 3 items, range 4–15, Cronbach's alpha=.69.

**Table 3.** Global perceived stress and prostate cancer risk by social support, perceived and control stress, and socioeconomic status indicators

|                                | <i>n</i> in Strata | Global Perceived Stress (GPS) Score Comparing          |                                                          |                                                                 |
|--------------------------------|--------------------|--------------------------------------------------------|----------------------------------------------------------|-----------------------------------------------------------------|
|                                |                    | Highest (GPS>20) with<br>Lowest (GPS<14)<br>OR (95%CI) | Middle (GPS 14–20) with<br>Lowest (GPS<14)<br>OR (95%CI) | Highest and Middle (≥14)<br>with Lowest GPS (<14)<br>OR (95%CI) |
| All men                        | 777                | .82 (.48–1.38)                                         | .95 (.70–1.29)                                           | .93 (.69–1.24)                                                  |
| African American men           | 318                | 1.18 (.47–2.63)                                        | .85 (.43–1.68)                                           | 1.20 (.75–1.92)                                                 |
| Caucasian men                  | 459                | .76 (.52–1.12)                                         | 1.33 (.81–2.18)                                          | .79 (.54–1.14)                                                  |
| GPS‡ by John Henryism (JH)*    |                    |                                                        |                                                          |                                                                 |
| High (JH score 29–30)          | 355                | .85 (.36–2.02)                                         | .92 (.59–1.43)                                           | .91 (.59–1.40)                                                  |
| Intermediate (JH score 25–28)  | 294                | 1.33 (.52–3.43)                                        | 1.18 (.73–1.93)                                          | 1.16 (.72–1.89)                                                 |
| Low (JH score 12–24)           | 128                | .58 (.19–1.83)                                         | .69 (.29–1.64)                                           | .67 (.29–1.53)                                                  |
| GPS‡ by Social Support (SS)†   |                    |                                                        |                                                          |                                                                 |
| High (SS score 15)             | 445                | .95 (.46–1.94)                                         | 1.23 (.83–1.81)                                          | 1.18 (.81–1.72)                                                 |
| Intermediate (SS score 12–14)  | 250                | .87 (.29–2.55)                                         | .66 (.38–1.13)                                           | .68 (.40–1.15)                                                  |
| Low (SS score 3–11)            | 75                 | .96 (.20–4.70)                                         | 1.11 (.25–4.88)                                          | 1.05 (.26–4.31)                                                 |
| GPS‡ by stage at diagnosis     |                    |                                                        |                                                          |                                                                 |
| Stage I–II / controls          | 295/383            | .97 (.56–1.67)                                         | .96 (.69–1.33)                                           | .96 (.70–1.31)                                                  |
| Stage III–IV / controls        | 99/383             | .55 (.20–1.53)                                         | .89 (.56–1.43)                                           | .85 (.54–1.34)                                                  |
| GPS‡ by education level        |                    |                                                        |                                                          |                                                                 |
| Less than high school graduate | 287                | 1.12 (.55–2.28)                                        | 1.78 (1.04–3.06)                                         | 1.56 (.93–2.62)                                                 |
| High school graduate           | 188                | .36 (.12–1.12)                                         | .66 (.35–1.23)                                           | .60 (.33–1.10)                                                  |
| College or technical school    | 298                | 2.76 (.54–14.18)                                       | .74 (.47–1.18)                                           | .80 (.50–1.26)                                                  |
| GPS‡ by income                 |                    |                                                        |                                                          |                                                                 |
| <\$40,000                      | 443                | .90 (.48–1.69)                                         | .99 (.65–1.50)                                           | .97 (.65–1.46)                                                  |
| ≥\$40,000                      | 230                | 2.61 (.26–26.26)                                       | .74 (.44–1.26)                                           | .77 (.46–1.30)                                                  |
| Missing                        | 104                | .51 (.13–2.03)                                         | 1.23 (.51–2.92)                                          | 1.04 (.45–2.37)                                                 |

Adjusted for age (categorical variable), South Carolina region (three areas), and race (African American or Caucasian).

\* John Henryism Scale: 6 items, range 10 to 30, Cronbach's alpha=.66.

† Social Support: 3 items, range 4–15, Cronbach's alpha=.69; 7 missing.

‡ Global Perceived Stress Scale: 7 items, range 7–29, Cronbach's alpha=.51.

classified based on case status. We used a measure of global perceived stress that does not measure the frequency and magnitude of specific stressful life events. The GPS scale requires a significant self-knowledge and ability to disclose individual vulnerability; this ability to disclose may be associated with higher education and greater social support. This measure of stress may not be an appropriate measure of stresses experienced but rather of stresses perceived. Life experiences may be a more germane factor to assess. All measures of stress, coping, and social support were self-reported because the individual is the best barometer of perceived stress, coping, and support. We used abbreviated measures for stress, coping, and social support, which may lead to some misclassification; however, the Cron-

bach's  $\alpha$  values for our measures were comparable to those reported for the full measures.<sup>37,43</sup> The Cronbach's  $\alpha$  values were lower than optimal, and this finding indicates the potential for misclassification, which may reduce ORs toward the null. Our measure of perceived stress, social support, and John Henryism in the year before the interview may cause the exposure measure to not reflect the etiologically relevant time period. However, determining that relevant time period is difficult as it may range from experiences in childhood through adulthood. Other limitations include a lower response rate among African Americans than Caucasians. The refusal rates did not differ by race, but the proportion that could not be located was higher among African American (19.3%) than

Caucasian (6%) men. Finally, this study had limited power to adequately evaluate several interactions.

This is the first population-based case-control study to address stress, coping, and social support and prostate cancer risk among both African American and Caucasian men. African American men may have higher prostate cancer rates because of genetic factors and environmental exposures, which may include environmental and individual stress, reactions to stress, and social support to buffer the effects of stress. We found that high-effort coping was more important than perceived stress as a correlate of prostate cancer risk, particularly among those with less social support. While the biologic effect of coping and support may be similar by race, the distribution of these risk

**Table 4. John Henryism Scores and prostate cancer risk by social support, perceived and control stress, and socioeconomic status indicators**

|                                                  | n in Strata | John Henryism Scale (JHS) Score* comparing                          |                                                                    |                                                                    |
|--------------------------------------------------|-------------|---------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------|
|                                                  |             | Highest (JHS 29–30) with<br>Lowest scores (JHS 12–24)<br>OR (95%CI) | Middle (JHS 25–28) with<br>Lowest scores (JHS 12–24)<br>OR (95%CI) | High and Middle (JHS<br>>24) with Lowest (JHS<br>12–24) OR (95%CI) |
| All men                                          | 777         | 1.51 (1.00–2.29)                                                    | 1.79 (1.17–2.73)                                                   | 1.63 (1.11–2.40)                                                   |
| African American men                             | 318         | 1.69 (.86–3.30)                                                     | 2.19 (1.07–4.48)                                                   | 1.52 (.94–2.48)                                                    |
| Caucasian men                                    | 459         | 1.44 (.85–2.44)                                                     | 1.61 (.52–1.36)                                                    | 1.86 (.97–3.55)                                                    |
| John Henryism* by Global Perceived Stress (GPS)† |             |                                                                     |                                                                    |                                                                    |
| High (GPS score >20)                             | 73          | 1.47 (.42–5.13)                                                     | 1.79 (.49–6.55)                                                    | 1.61 (.53–4.87)                                                    |
| Intermediate (GPS score 14–20)                   | 416         | 1.52 (.77–2.68)                                                     | 1.93 (1.09–3.42)                                                   | 1.71 (1.01–2.89)                                                   |
| Low (GPS score 7–13)                             | 288         | 1.21 (.55–2.64)                                                     | 1.18 (.53–2.65)                                                    | 1.20 (.57–2.54)                                                    |
| John Henryism* by Social Support (SS)†           |             |                                                                     |                                                                    |                                                                    |
| High (SS score 15)                               | 445         | .62 (.32–1.18)                                                      | .75 (.39–1.47)                                                     | .67 (.36–1.25)                                                     |
| Intermediate (SS score 12–14)                    | 250         | 2.98 (1.42–6.25)                                                    | 3.69 (1.80–7.55)                                                   | 3.35 (1.71–6.55)                                                   |
| Low (SS score 3–11)                              | 75          | 2.10 (.60–7.33)                                                     | 2.06 (.63–6.78)                                                    | 2.08 (.71–6.07)                                                    |
| John Henryism* by stage at diagnosis             |             |                                                                     |                                                                    |                                                                    |
| Stage I–II / controls                            | 290/383     | 1.45 (.93–2.28)                                                     | 1.86 (1.18–2.94)                                                   | 1.63 (1.07–2.49)                                                   |
| Stage III–IV / controls                          | 99/383      | 1.72 (.88–3.38)                                                     | 1.56 (.77–3.14)                                                    | 1.65 (.87–3.13)                                                    |
| John Henryism* by education                      |             |                                                                     |                                                                    |                                                                    |
| Less than high school graduate                   | 287         | 1.14 (.56–2.33)                                                     | 1.71 (.81–3.63)                                                    | 1.34 (.68–2.65)                                                    |
| High School graduate                             | 188         | 1.65 (.71–3.84)                                                     | 1.68 (.69–4.09)                                                    | 1.67 (.74–3.71)                                                    |
| College or technical school                      | 298         | 1.67 (.87–3.21)                                                     | 1.82 (.97–3.42)                                                    | 1.75 (.98–3.15)                                                    |
| John Henryism* by income                         |             |                                                                     |                                                                    |                                                                    |
| <\$40,000                                        | 443         | 1.57 (.92–2.67)                                                     | 1.56 (.89–2.73)                                                    | 1.56 (.94–2.59)                                                    |
| ≥\$50,000                                        | 230         | 1.34 (.59–3.03)                                                     | 2.32 (1.04–5.19)                                                   | 1.81 (.85–3.86)                                                    |
| Missing                                          | 104         | 1.46 (.48–4.44)                                                     | 1.90 (.62–5.90)                                                    | 1.65 (.59–4.63)                                                    |

Adjusted for age (categorical variable), South Carolina region (three areas), and race (African American or Caucasian).

\* John Henryism Scale: 6 items, range 10 to 30, Cronbach = .66.

† Social Support: 3 items, range 4–15, Cronbach = .69; 7 missing.

‡ Global Perceived Stress Scale: 7 items, range 7–29, Cronbach = .51.

factors, and particularly economic support, may differ markedly by race and possibly explain part of the racial difference in prostate cancer incidence. Further research is needed to explore the interactions between stress, coping, and forms of support and prostate cancer risk. These studies need to include sufficient numbers of African American men to explore interactions in this high-risk group. Additional research with

multiple measures of stress, coping, and support, including biologic measures, could further explore any biologic mechanisms by which stress, coping, and support may be etiologically linked with prostate cancer.

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*Design concept of study:* Coker, Sanderson, Ellison

*Acquisition of data:* Coker, Sanderson, Ellison

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# A Multilevel Analysis of Socioeconomic Status and Prostate Cancer Risk

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**PURPOSE:** We investigated whether prostate cancer was associated with socioeconomic status (SES) at the individual level, area level, or a combination of both levels.

**METHODS:** This population-based case-control study of prostate cancer in men aged 65 to 79 years was conducted between 2000 and 2002 in South Carolina. Complete interviews were available for 407 incident prostate cancer cases and 393 controls (with respective response rates of 61% and 64%). We used educational level to measure individual-level SES and a composite variable capturing income and education from 2000 Census data to measure area-level SES.

**RESULTS:** After adjustment for race, age, geographic region, and prostate-specific antigen testing, men with some college were at reduced risk for prostate cancer (odds ratio [OR], 0.44; 95% confidence interval [CI], 0.27–0.72), as were men in the highest quartile of area-level SES (OR, 0.52; 95% CI, 0.34–0.80). When assessing individual-level and area-level SES simultaneously and accounting for their nonindependence, the independent negative associations persisted and appeared to be more striking for men with a diagnosis of localized disease, rather than advanced disease.

**CONCLUSION:** The independent effects of area-level and individual-level SES on prostate cancer risk seen in our study may help explain the conflicting results of previous studies conducted at both levels.

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**KEY WORDS:** Prostate Cancer, Socioeconomic Status, Multilevel Analysis, Case-Control Studies.

## INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer in the United States and the second leading cause of cancer deaths among men. Little is understood about the cause of prostate cancer, and we do not know what factors might explain why African-American men are at greater risk relative to white men. Several studies investigated prostate cancer incidence associated with individual-level socioeconomic status (SES) based on income, occupation, or educational level, with conflicting results. We limit our review to studies conducted in the United States because SES levels differ across countries. Two of the four studies that evaluated the association between individual-level SES and prostate cancer incidence in the United States reported positive associations (1, 2), whereas two studies reported no association

(3, 4). Of the seven studies that investigated area-level SES and prostate cancer incidence in the United States, three studies each reported a positive association (5–7) or no association (8–10), whereas one study reported a negative association (11). Proposed mechanisms for explaining the positive association between individual-level and area-level SES and prostate cancer are consuming a healthy diet (4), engaging in exercise (4), and increased access to screening (12).

Studies of SES and prostate cancer must account for screening because the effect of high SES on prostate cancer risk may have differed before and after the advent of prostate-specific antigen (PSA) testing. Before PSA testing, men with higher SES were more likely to have lower rates of prostate cancer as a result of engaging in healthy behaviors (4). After PSA testing, men with higher SES were more likely to be screened annually (12) and thus the disease was more likely to be diagnosed, especially at an earlier stage (13). Using 1987 as the year that PSA testing became widespread, the majority of individual-level (1, 2, 4) and half the area-level (8–11) studies of SES and prostate cancer were conducted before screening, which may help explain the mixed results.

Along with the failure to account for PSA testing, another possible explanation for the mixed results of the SES and prostate cancer association is the failure to account for area-level SES in studies of individual-level SES, and vice versa. Several studies investigated the joint effects of

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### Selected Abbreviations and Acronyms

CI = confidence interval  
OR = odds ratio  
PSA = prostate-specific antigen  
SES = socioeconomic status

individual-level and area-level SES and cardiovascular disease incidence (14, 15) and mortality (16, 17); however, few focused on cancer (17–19). Robert et al. (18) recently investigated the joint effect of individual-level and area-level SES on breast cancer incidence and found that area-level SES was associated positively with breast cancer after adjustment for individual-level SES, whereas the reverse was not true. Conversely, Steenland et al. (19) found little effect of area-level SES on prostate cancer mortality after adjustment for individual-level SES. Borrell et al. (17) found greater rates of cancer mortality among blacks and whites in the Atherosclerosis Risk in Communities Study who resided in neighborhoods with the lowest SES score that was weakened by adjustment for individual-level SES. To our knowledge, no other study simultaneously investigated the effect of individual-level and area-level measures of SES on prostate cancer risk. We assess joint effects of area-level and individual-level SES to indirectly determine whether conflicting results for prostate cancer incidence associated with individual-level SES may have been caused by the unmeasured influence of area-level SES.

## METHODS

Detailed methods of this population-based case-control study conducted in South Carolina from 2000 to 2002 appear elsewhere (20). Briefly, cases diagnosed with primary invasive prostate cancer between October 1999 and September 2001 were identified through the South Carolina Central Cancer Registry. During this time, the South Carolina Central Cancer Registry was certified as silver by the North American Association of Central Cancer Registries, with a case ascertainment rate between 90% and 95% (21). Eligible cases were South Carolina residents who were Caucasian or African American, aged 65 to 79 years, and had histologically confirmed prostate cancer and for whom physicians had given permission for research staff to contact the patient. We selected all eligible cases with advanced disease (stages III and IV) and a random sample of men with localized disease (stages I and II). We had insufficient funding to study all men with localized disease. Because we wanted approximately equal numbers of men with localized disease by race, we performed stratified sampling by race and oversampled African-American men by randomly selecting 82% of men with localized disease compared with 40% of Caucasian men with localized disease. Of 692 eligible

prostate cancer cases, 425 (61.4%) completed a standardized telephone interview. Of the remaining eligible cases, 90 physicians refused (13.0%), 71 patients refused (10.3%), 24 patients died before the interview (3.5%), 59 patients were not located (8.5%), and 23 patients were too sick to participate (3.3%).

Control subjects were randomly sampled from the 1999 Health Care Financing Administration Medicare beneficiary file. Controls were frequency matched to cases for age (5-year age groups), race (Caucasian and African American), and geographic region (western 14 counties, middle 19 counties, and eastern 13 counties of the state). Eligible controls were South Carolina residents aged 65 to 79 years with no history of prostate cancer. Of 756 eligible controls, 482 (63.8%) completed the interview. Of the remaining eligible controls, 108 controls refused (14.3%), 22 controls died before the interview (2.9%), 112 controls were not located (14.8%), and 32 controls were too sick to participate (4.2%). We eliminated 59 subjects (7 cases and 52 controls) who upon review of medical records were determined to have prevalent prostate cancer. After excluding an additional 48 subjects (11 cases and 37 controls) who completed fewer than 10 questions, the final sample size was 800 subjects (407 cases and 393 controls).

Institutional Review Boards of the University of South Carolina, Centers for Disease Control and Prevention, and National Cancer Institute approved this project's data collection procedures. Interviewing began in June 2000 and was completed in August 2002. Trained interviewers from the University of South Carolina Survey Research Laboratory conducted computer-assisted telephone interviews with subjects who provided verbal consent with the understanding that written consent would be obtained. The questionnaire collected information on demographic characteristics, SES, stress, coping, alcohol and tobacco use, physical activity, diet, medical history, family history of cancer, history of sexually transmitted diseases, and farm-related work activities and exposures. Most exposures pertained to the period before a reference date, the date of diagnosis for cases and an assigned date for controls that was similar to the distribution of diagnosis dates among cases.

We used the generalized linear latent and mixed models macro in STATA 8 (StataCorp LP, College Station, Texas) to estimate the odds ratio (OR) of prostate cancer associated with individual-level and area-level SES while accounting for their nonindependence and controlling for potential confounding factors (22). We had a two-level hierarchical structure; therefore, we fit a two-random level intercepts logistic model and used RESET diagnostic test to evaluate misspecification of error or inappropriate link function (23). Because the majority of men were retired, we used educational level to measure individual-level SES, rather than annual household income 1 year before diagnosis.

There were five categories of educational level: (i) less than eighth grade, (ii) 9th to 11th grade, (iii) high school graduate, (iv) some college or technical school, and (v) college graduate or more. To measure area-level SES, we created a composite variable consisting of median household income, percentage of persons living below the poverty level, percentage unemployment, and percentage of college or higher educational attainment addressing four of the six domains thought to comprise socioeconomic position in the United States (24). Subjects' addresses were not geocoded; therefore, this information was available at the ZIP code level from the 2000 census (25). Of the total of 919 ZIP codes in South Carolina, 265 were represented in the study. To ensure sufficient sample sizes and minimize overdispersion of estimates, we collapsed ZIP codes of homogeneous geographic and demographic characteristics into groups with a minimum of 25 subjects in each. There were 21 groupings ranging from 29 to 57 subjects (median = 41). We reversed the coding of poverty level and unemployment, summed the four area-level measures of SES, and categorized the composite variable by using the quartile distribution among controls. Cronbach  $\alpha$  for this composite variable was 0.83 among controls, indicating these items went together in measuring the area-level SES construct.

Individual-level variables assessed as confounders included marital status, family history of prostate cancer, body mass index, and frequency of PSA testing, as categorized in Table 1. Body mass index, defined as self-reported weight in kilograms before reference date divided by the square of self-reported height in meters, was categorized by using the quartile distribution among controls. PSA testing was categorized as frequency within the past 5 years, with men who reported they had a PSA test performed, but did not remember the number of tests, categorized as one to two tests (53 local cases, 10 advanced cases, 90 controls). Controls were frequency matched to cases on age, race, and geographic region; thus, we adjusted for these three factors based on the study design. We also adjusted for PSA testing because it was the only variable to materially change unadjusted ORs. Although PSA testing may be in the causal pathway between SES and prostate cancer, we adjusted for it to investigate the association between SES and prostate cancer, accounting for the effect of SES on PSA testing. In analyses by stage at diagnosis, men with stages I and II were classified as having localized disease, and men with stages III and IV were classified as having advanced disease. Stages I and II correspond to tumors that were clinically unapparent or confined within the prostate with no nodal involvement or metastases (26). Stages III and IV correspond to tumors that extended through the prostatic capsule or invaded adjacent structures with or without nodal involvement or metastases. Linear trend was assessed by treating categorical variables as continuous variables.

**TABLE 1.** Comparison of cases by stage at diagnosis and controls for demographic and socioeconomic factors

|                                                        | Localized cases<br>(n = 314)<br>N (%) | Advanced cases<br>(n = 102)<br>N (%) | Controls<br>(n = 429)<br>N (%) |
|--------------------------------------------------------|---------------------------------------|--------------------------------------|--------------------------------|
| Race                                                   |                                       |                                      |                                |
| Caucasian                                              | 175 (55.7)                            | 70 (68.6)                            | 258 (60.1)                     |
| African-American                                       | 139 (44.3)                            | 32 (31.4)                            | 171 (39.9)                     |
| Age (years)                                            |                                       |                                      |                                |
| 65–69                                                  | 138 (44.0)                            | 54 (52.9)                            | 186 (43.4)                     |
| 70–74                                                  | 102 (32.5)                            | 32 (31.4)                            | 125 (29.1)                     |
| 75–79                                                  | 74 (23.5)                             | 16 (15.7)                            | 118 (27.5)                     |
| Geographic region                                      |                                       |                                      |                                |
| Eastern counties                                       | 180 (57.3)                            | 55 (53.9)                            | 243 (56.6)                     |
| Middle counties                                        | 81 (25.8)                             | 26 (25.5)                            | 92 (21.5)                      |
| Western counties                                       | 53 (16.9)                             | 21 (20.6)                            | 94 (21.9)                      |
| Marital status <sup>a</sup>                            |                                       |                                      |                                |
| Single/separated/<br>divorced/widowed                  | 56 (18.6)                             | 17 (17.0)                            | 80 (20.6)                      |
| Married/living as married                              | 245 (81.4)                            | 83 (83.0)                            | 308 (79.4)                     |
| Missing                                                | 5                                     | 1                                    | 5                              |
| Family history <sup>a</sup>                            |                                       |                                      |                                |
| None                                                   | 212 (70.9)                            | 66 (66.7)                            | 329 (84.6)                     |
| First-degree                                           | 63 (21.1)                             | 23 (23.2)                            | 43 (11.0)                      |
| Second-degree                                          | 24 (8.0)                              | 10 (10.1)                            | 17 (4.4)                       |
| Missing                                                | 7                                     | 2                                    | 4                              |
| Body mass index (quartiles) <sup>a</sup>               |                                       |                                      |                                |
| < 24.4                                                 | 77 (25.9)                             | 13 (13.1)                            | 90 (23.5)                      |
| 24.4–27.2                                              | 83 (28.0)                             | 31 (31.3)                            | 101 (26.3)                     |
| 27.3–29.8                                              | 69 (23.2)                             | 27 (27.3)                            | 96 (25.1)                      |
| ≥ 29.9                                                 | 68 (22.9)                             | 28 (28.3)                            | 96 (25.1)                      |
| Missing                                                | 9                                     | 2                                    | 10                             |
| No. of prostate-specific antigen tests in past 5 years |                                       |                                      |                                |
| 0                                                      | 43 (13.7)                             | 18 (17.7)                            | 98 (22.9)                      |
| 1–2                                                    | 102 (32.5)                            | 29 (28.4)                            | 154 (36.0)                     |
| 3–4                                                    | 48 (15.3)                             | 19 (18.6)                            | 66 (15.4)                      |
| ≥ 5                                                    | 121 (38.5)                            | 36 (35.3)                            | 110 (25.7)                     |
| Missing                                                | 1                                     | 0                                    | 0                              |
| Educational level                                      |                                       |                                      |                                |
| Elementary education                                   | 84 (26.8)                             | 22 (22.2)                            | 89 (20.7)                      |
| Some high school                                       | 44 (14.1)                             | 11 (11.1)                            | 69 (16.1)                      |
| High school graduate                                   | 78 (24.9)                             | 23 (23.2)                            | 102 (23.8)                     |
| Some college or technical<br>school                    | 37 (11.8)                             | 17 (17.2)                            | 77 (18.0)                      |
| College graduate                                       | 70 (22.4)                             | 26 (26.3)                            | 92 (21.5)                      |
| Missing                                                | 1                                     | 3                                    | 0                              |
| Composite socioeconomic status (quartiles)             |                                       |                                      |                                |
| Low                                                    | 105 (33.4)                            | 30 (29.4)                            | 118 (27.5)                     |
| Medium                                                 | 94 (29.9)                             | 18 (17.7)                            | 115 (26.8)                     |
| High                                                   | 71 (22.6)                             | 35 (34.3)                            | 106 (24.7)                     |
| Very high                                              | 44 (14.0)                             | 19 (18.6)                            | 90 (21.0)                      |

<sup>a</sup>Consists of 306 local cases, 101 advanced cases, and 393 controls.

## RESULTS

Table 1 lists cases by stage at diagnosis and controls for demographic and socioeconomic factors. Compared with controls, prostate cancer cases were more likely to be younger, reside in the middle portion of the state, be married or living

as married, have a family history of prostate cancer, have undergone PSA testing, have a lower educational level themselves, and live in a community with a lower composite SES. A greater percentage of men with a diagnosis of localized disease were African American and in the lowest quartile of body mass index than men with a diagnosis of advanced disease, whereas the reverse was true of men with a diagnosis with advanced disease.

ORs and 95% confidence intervals (CIs) for prostate cancer associated with individual-level and area-level SES are listed in Table 2. There were significant correlations between PSA testing and individual-level (Spearman  $r = 0.30$ ;  $p < 0.0001$ ) and area-level (Spearman  $r = 0.09$ ;  $p = 0.007$ ) SES (data not shown). After adjustment for race, age, geographic region, and PSA testing, men with some college or technical school were at significantly reduced risk (OR, 0.44; 95% CI, 0.27-0.72) and college graduates were at borderline reduced risk (OR, 0.67; 95% CI, 0.42-1.05) for prostate cancer. Combining these upper two categories resulted in a significantly reduced risk for prostate cancer (OR, 0.55; 95% CI, 0.35-0.87). Similarly, men in the highest quartile of area-level SES (OR, 0.52; 95% CI, 0.34-0.80) were at reduced prostate cancer risk. In both measures of SES, there was a trend of decreasing risk with increasing educational level. Although the trend test was significant for individual-level SES, it must be noted that the referent group was markedly higher than all other educational groups and the trend test is driven by this group. Additional adjusting for individual-level or area-level SES and accounting for the nonindependence of these measures resulted in independent negative associations for prostate cancer in men with some college (OR, 0.45; 95% CI, 0.27-0.78) and men in the highest quartile of area-level SES (OR, 0.52; 95% CI, 0.25-1.10).

Risk for prostate cancer associated with socioeconomic factors by stage at diagnosis is listed in Table 3. With one exception, the third quartile of area-level SES in men diagnosed with advanced disease, there were reductions in risk associated with individual-level and area-level SES regardless of stage at diagnosis. The decreased risk for men with some college or technical school and men who lived in the highest quartile of area-level SES was weaker for men with a diagnosis of advanced cancer than those with a diagnosis of localized cancer, but remained reduced even after adjustment for the other level measure of SES.

## DISCUSSION

We found a significantly reduced risk for prostate cancer associated with having some college or technical school and a borderline reduced risk for the highest category of our individual-level SES measure, educational level. In addition, there was a significant trend of decreasing risk with increasing educational level. A possible explanation for the trend is the greater percentage of cases (especially those with localized disease) with an elementary education than controls. Although not limited to men with a diagnosis of localized disease, the reduction in risk in the two highest SES categories was more pronounced for this group. Our results are in conflict with the majority of studies of individual-level SES and prostate cancer risk, which reported a positive (1, 2) or no association (3, 4). Possible explanations for our findings relate to the educational level and race of men in our study. Men in our study had a fairly low SES; 36.8% of our controls aged 65 and older had less than a high school education in comparison to 31.2% of men in the United States in 1999 (27). The only study of

**TABLE 2.** Odds ratios for prostate cancer associated with individual-level and area-level socioeconomic factors

|                                            | OR <sup>a</sup> (95% CI) | OR <sup>b</sup> (95% CI) | OR <sup>c</sup> (95% CI) |
|--------------------------------------------|--------------------------|--------------------------|--------------------------|
| Educational level                          |                          |                          |                          |
| Elementary education                       | 1.00 (Referent)          | 1.00 (Referent)          |                          |
| Some high school                           | 0.60 (0.37-0.95)         | 0.57 (0.34-0.94)         |                          |
| High school graduate                       | 0.69 (0.45-1.06)         | 0.70 (0.44-1.11)         |                          |
| Some college or technical school           | 0.44 (0.27-0.72)         | 0.45 (0.27-0.78)         |                          |
| College graduate                           | 0.67 (0.42-1.05)         | 0.65 (0.39-1.07)         |                          |
| <i>p</i> for trend                         | 0.05                     | 0.08                     |                          |
| Composite socioeconomic status (quartiles) |                          |                          |                          |
| Low                                        | 1.00 (Referent)          |                          | 1.00 (Referent)          |
| Medium                                     | 0.79 (0.53-1.17)         |                          | 0.78 (0.38-1.59)         |
| High                                       | 0.86 (0.58-1.28)         |                          | 0.96 (0.42-2.23)         |
| Very high                                  | 0.52 (0.34-0.80)         |                          | 0.52 (0.25-1.10)         |
| <i>p</i> for trend                         | <0.01                    |                          | 0.13                     |

OR = odds ratio; CI = confidence interval.

<sup>a</sup>Adjusted for race, age, geographic region, and prostate-specific antigen testing.

<sup>b</sup>Adjusted for race, age, geographic region, composite socioeconomic status, and prostate-specific antigen testing.

<sup>c</sup>Adjusted for race, age, geographic region, educational level, and prostate-specific antigen testing.

**TABLE 3.** Odds ratios for prostate cancer associated with individual-level and area-level socioeconomic factors by stage at diagnosis

|                                            | OR <sup>a</sup> (95% CI) | OR <sup>b</sup> (95% CI) | OR <sup>c</sup> (95% CI) |
|--------------------------------------------|--------------------------|--------------------------|--------------------------|
| <b>Localized</b>                           |                          |                          |                          |
| Educational level                          |                          |                          |                          |
| Elementary education                       | 1.00 (Referent)          | 1.00 (Referent)          |                          |
| Some high school                           | 0.60 (0.36–0.98)         | 0.54 (0.31–0.93)         |                          |
| High school graduate                       | 0.70 (0.44–1.11)         | 0.70 (0.43–1.16)         |                          |
| Some college or technical school           | 0.39 (0.22–0.67)         | 0.41 (0.23–0.73)         |                          |
| College graduate                           | 0.62 (0.38–1.02)         | 0.61 (0.35–1.05)         |                          |
| <i>p</i> for trend                         | 0.03                     | 0.06                     |                          |
| Composite socioeconomic status (quartiles) |                          |                          |                          |
| Low                                        | 1.00 (Referent)          |                          | 1.00 (Referent)          |
| Medium                                     | 0.87 (0.58–1.32)         |                          | 0.88 (0.40–1.96)         |
| High                                       | 0.72 (0.47–1.11)         |                          | 0.80 (0.35–1.83)         |
| Very high                                  | 0.48 (0.30–0.76)         |                          | 0.51 (0.21–1.21)         |
| <i>p</i> for trend                         | <0.01                    |                          | 0.10                     |
| <b>Advanced</b>                            |                          |                          |                          |
| Educational level                          |                          |                          |                          |
| Elementary education                       | 1.00 (Referent)          | 1.00 (Referent)          |                          |
| Some high school                           | 0.54 (0.24–1.21)         | 0.61 (0.26–1.42)         |                          |
| High school graduate                       | 0.67 (0.33–1.34)         | 0.69 (0.32–1.45)         |                          |
| Some college or technical school           | 0.58 (0.27–1.25)         | 0.54 (0.24–1.26)         |                          |
| College graduate                           | 0.77 (0.37–1.59)         | 0.74 (0.34–1.64)         |                          |
| <i>p</i> for trend                         | 0.62                     | 0.49                     |                          |
| Composite socioeconomic status (quartiles) |                          |                          |                          |
| Low                                        | 1.00 (Referent)          |                          | 1.00 (Referent)          |
| Medium                                     | 0.56 (0.28–1.10)         |                          | 0.57 (0.24–1.36)         |
| High                                       | 1.32 (0.72–2.40)         |                          | 1.41 (0.63–3.17)         |
| Very high                                  | 0.72 (0.37–1.39)         |                          | 0.66 (0.26–1.65)         |
| <i>p</i> for trend                         | 0.84                     |                          | 0.74                     |

OR = odds ratio; CI = confidence interval.

<sup>a</sup>Adjusted for race, age, geographic region, and prostate-specific antigen testing.

<sup>b</sup>Adjusted for race, age, geographic region, composite socioeconomic status, and prostate-specific antigen testing.

<sup>c</sup>Adjusted for race, age, geographic region, educational level, and prostate-specific antigen testing.

individual-level SES and prostate cancer conducted since the advent of PSA testing found no association after adjustment for PSA testing for the highly educated, younger American Cancer Society Nutrition Cohort Study; 8% of their participants aged 55 years and older had less than a high school education (3) compared with 26% of men in the United States in 1999 (27). A large percentage of men in our study were African American (40.8% of cases; 42.2% of controls). Yu et al. (2) reported a weak positive association between college education and prostate cancer risk for Caucasian men, but not African-American men.

Similarly, prostate cancer was associated negatively with area-level SES measured by using our composite variable. Again, the reduction in risk was stronger for men with a diagnosis of localized disease than those with a diagnosis of advanced disease. The negative association we found was in contrast to most previous studies of area-level SES and prostate cancer that reported a positive association (5–7) or no association (8–10). In their study of area-level SES and prostate cancer mortality using the American Cancer Society Nutrition Cohort Study, Steenland et al. (K. Steenland, personal communication, February 9, 2006) found a positive

association. Possible explanations for our findings relate to the race of men in our study and the different measures of area-level SES used by different studies. As indicated, more than 40% of our participants were African American. One study identified a positive association in all racial groups except whites (6), another study found a positive association in all racial groups except Asians (8), and another study reported no association in African-American or Caucasian men (9). Studies of area-level SES used a variety of measures, including a combination of occupation and poverty level (5), median household income (6), a combination of median household income and educational attainment (7), and a combination of household income, home value, occupation, and education (19).

After performing a multilevel analysis, there was little effect on either measure of SES with approximately the same reduction in prostate cancer risk associated with the two highest levels of individual-level SES combined (OR, 0.55; 95% CI, 0.35–0.87) as the highest quartile of area-level SES (OR, 0.52; 95% CI, 0.25–1.10). These results were evident for men with a diagnosis of localized and advanced disease; however, the association was more

pronounced for men with localized disease. This is in contrast to the majority of studies of SES and cardiovascular disease incidence and mortality, which reported stronger associations for individual-level SES than area-level SES after simultaneous adjustment (14–17). In the American Cancer Society Nutrition Cohort Study, Steenland et al. (K. Steenland, personal communication, February 9, 2006) found no association between individual-level SES and prostate cancer mortality after adjustment for area-level SES and vice versa. However, the only study of cancer incidence to examine the joint effects of individual-level and area-level SES reported a stronger effect of area-level SES than individual-level SES (18). These investigators hypothesized that the stronger positive effect of area-level than individual-level SES they saw on breast cancer risk may have been caused by greater access to mammograms in higher SES areas (28) or to physical and environmental characteristics common in the community that may increase a woman's breast cancer risk. One possible explanation for the reduced prostate cancer risk associated with higher individual-level and area-level SES we saw is that men with higher SES and those living in higher SES areas are less likely to undergo PSA testing. This was not the case in our study in which PSA testing positively and significantly correlated with both measures of SES (individual-level SES, Spearman  $r = 0.30$ ,  $p < 0.0001$ ; area-level SES, Spearman  $r = 0.09$ ,  $p = 0.007$ ). An alternative explanation for the reduced risk for prostate cancer associated with high individual-level and area-level SES is that men with higher SES and those from higher SES areas have greater access to healthful diets and physical activity.

This study was not without limitations. Our response rates were less than desired, and we sampled men with localized disease, somewhat limiting the generalizability of our results and possibly resulting in some nonsignificant reductions in prostate cancer risk. African-American men with advanced disease were less likely to participate than African-American men with localized disease, which limited study power to statistically assess effect modification by race and stage. We were unable to determine whether nonparticipation rates of cases and controls differed by SES. However, similar percentages of nonrespondents (22.6%) and respondents (25.2%) had diagnoses of advanced disease, which would argue against selective survival of cases. The average time between diagnosis and interview was 8.7 months, which may have led to misclassification. Another source of misclassification was the memory problems common in men aged 65 years and older. Our study power was limited for some joint effects because of small numbers. We were unable to assess race as an effect modifier of the association between SES and prostate cancer because of small numbers. Analysis at the grouped ZIP code level in our study may not reflect

the area-level SES accurately because SES of block groups and census tracts within ZIP codes tend to vary substantially (24). Although block groups and census tracts may better represent area-level SES than grouped ZIP codes, we chose to group ZIP codes to provide stable estimates.

Our study is the first population-based case-control study of prostate cancer to simultaneously assess the effect of individual-level and area-level SES on prostate cancer risk. Additional strengths of the study include the fairly large number of men with advanced disease, which allowed us to perform analyses by stage at diagnosis, and use of an accepted measure of area-level SES (24). We adjusted for the frequency of PSA testing in an attempt to isolate the effect of SES apart from its influence on access to care. Area-level SES may be a more comprehensive measure of SES than individual-level SES because it captures social characteristics of communities that are not typically measured (29). The independent effects of area-level and individual-level SES on prostate cancer risk seen in our study may help explain the conflicting results of previous studies conducted at both levels and would argue for the measurement of both levels in future studies.

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# Perinatal Factors and Mortality from Breast Cancer

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## Abstract

Inverse associations have been reported between birthweight and subsequent mortality from circulatory disease and diabetes among women. In the current study, we assessed whether perinatal factors were associated with mortality from breast cancer. This follow-up study consists of breast cancer cases who participated in two population-based case-control studies of breast cancer in women under age 45 years conducted between 1983 and 1992 in three western Washington counties. This analysis is restricted to the 1,024 cases or their proxies who completed a supplementary questionnaire on perinatal factors from 1994 to 1996. The mean and median length of follow-up among living cohort members were 153 and 148 months, respectively. Relative to women who were firstborn, women who were born second

or higher in the birth order seemed to have lower mortality from breast cancer [hazard ratio (HR), 0.2; 95% confidence interval (95% CI), 0.2-0.3]. In contrast, maternal age of  $\geq 35$  years (HR, 1.7; 95% CI, 1.1-2.8) was associated with higher breast cancer mortality relative to a maternal age of  $< 25$  years. Birth order modified the effect of maternal age on mortality from breast cancer ( $P = 0.03$ ). There was evidence of increased breast cancer mortality for birthweight of  $\geq 4,000$  g (HR, 1.8; 95% CI, 1.0-3.1) and twin membership (HR, 2.5; 95% CI, 1.0-6.2). The protective effect of being born second or higher in the birth order against breast cancer mortality regardless of maternal age is striking and needs to be confirmed in future studies. (Cancer Epidemiol Biomarkers Prev 2006;15(10):1984-7)

## Introduction

Reported associations between perinatal factors and breast cancer incidence have been mixed. In a review article, Potischman and Troisi (1) identified a strong elevation in breast cancer risk for being a twin and a moderate increase in premenopausal breast cancer risk for high birthweight. Results were inconsistent for breast cancer associated with being firstborn, older maternal age, and gestational age, whereas there was no relation for maternal smoking. Our previous studies conducted among the same group of younger women as in the present study (2, 3) and studies conducted since the review article have been in general agreement. Trichopoulos (4) hypothesized that exposure to high pregnancy estrogen levels *in utero* could lead to subsequent breast cancer, whereas exposure to low pregnancy estrogen levels could protect against subsequent breast cancer. In studies utilizing cord blood, Troisi et al. (5) and Shibata et al. (6) found no association between estrogen levels and high birthweight or being firstborn. Troisi et al. (5) did not report any association between estrogen levels and older maternal age; however, Shibata et al. (6) reported a positive association between estrogen levels and older maternal age. Alternative mechanisms that may explain associations between high birthweight and breast cancer incidence include higher intrauterine exposure to insulin (7-9), insulin-like growth factor I (7-9), or leptin (9) based on cord blood levels. To our knowledge, there

have been no studies of associations between cord blood levels of insulin, insulin-like growth factor I, or leptin and other perinatal factors.

Hypothesized pathways for breast cancer etiology could also influence the risk of dying although little research has been conducted to date. Goodwin et al. (10) found that elevated insulin levels, but not estrogen or insulin-like growth factor I levels, were associated with breast cancer mortality among women diagnosed pre- and postmenopausally independent of obesity. However, Borugian et al. (11) reported increased mortality from breast cancer associated with elevated insulin levels among women diagnosed postmenopausally only. To date, there have been no studies of leptin and breast cancer mortality. Only two studies have assessed the association between a perinatal factor and breast cancer mortality. In the Hertfordshire Cohort Study, Syddall et al. (12) failed to find an association between high birthweight and breast cancer mortality. In the American Cancer Society Cancer Prevention Study 1, Holmberg et al. (13) reported a nonsignificant elevation in breast cancer mortality associated with older maternal age. The present study was conducted to investigate the association between perinatal factors that may reflect estrogen, insulin, insulin-like growth factor I, and leptin levels and mortality from breast cancer.

## Materials and Methods

Breast cancer cases (or proxies for deceased cases) from two previous population-based case-control studies of breast cancer, among women under age 45 years diagnosed between January 1983 and December 1992 in three western Washington counties, were recontacted and asked to provide information pertaining to their birth. Detailed methods of the two studies appear elsewhere (14, 15). Briefly, women were eligible for the first study if they were diagnosed with primary invasive breast cancer between January 1983 and April 1990, were born after

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1944, and resided in King, Pierce, or Snohomish counties of Washington State at the time of diagnosis. Using the same methods as the first study, eligible study participants in the second study consisted of women who were diagnosed with primary invasive breast cancer from May 1990 to December 1992, were under age 45 years, and resided in the three county area. A total of 83% of eligible breast cancer cases ascertained through a population-based cancer registry completed a standardized personal interview in the initial studies. After obtaining ethical approval for the study of human subjects, all invasive breast cancer cases and proxies for deceased cases were targeted for the follow-up study. Between May 1994 and December 1996, a total of 1,024 (82.3%) mailed questionnaires or telephone interviews were completed for 1,244 eligible cohort members. Response rates were comparable for the 852 living cases (82.4%) and the 172 proxies for deceased cases (81.9%).

The study was approved by the institutional review board of the Fred Hutchinson Cancer Research Center. Although information on perinatal factors was also collected from mothers of cases, the small number of cases ( $n = 510$ ) with maternal information would have decreased the precision of estimates; therefore, this analysis is based on self-report of cases or their proxies.

After obtaining informed consent, women were asked about their birthweight in pounds and ounces or, if they could not recall their exact birthweight, whether they were  $<5.5$  or  $\geq 9$  pounds. Pounds and ounces were converted to grams;  $<5.5$  pounds was classified as  $<2,500$  g and  $\geq 9$  pounds was classified as  $\geq 4,000$  g. Maternal age was in exact years. Birth order was the combination of live and still births before the subject's birth. To classify gestational age, women were asked whether they were born  $>4$  weeks before they were due, around the time they were due, or  $>4$  weeks after they were due. Twin birth, maternal smoking, and maternal hormone use were yes or no questions. Maternal hormone use could have been use of diethylstilbestrol or any other hormonal formulation, such as oral contraceptives, during pregnancy with the subject. We conducted a validity study among women born in Washington state and found very high correlations comparing self-report with birth certificate for maternal age ( $r = 0.95$ ) and comparing self-report with mother report for birth order ( $r = 0.89$ ) and for birthweight ( $r = 0.85$ ; ref. 16).

Detailed methods of the follow-up for mortality appear elsewhere (17). Briefly, the primary source of information on deaths was the cancer registry, which attempts to update disease status and vital status on an annual basis. Information on death was collected for women who currently did and did not reside inside the cancer registry catchment area. Secondary sources of information on deaths were death certificates, National Death Index, Health Care Financing Administration tapes, and relatives of patients. Death certificates were abstracted to ascertain cause of death. After comparing the 92% of women whose death was breast cancer related with all-cause mortality among the entire cohort of women, we found similar results; thus, we report results for all-cause mortality. Subjects were followed until the earliest of the date of death, date last known to be alive, or end date of the follow-up period, which was June 2002. Of women not reported to be dead in June 2002, 93% of women had been located within the previous year and 96% had been located within the previous 3 years. The mean and median length of follow-up for living cohort members were 153 and 148 months, respectively.

Cox proportional hazards was used to estimate the relative risk of dying from breast cancer and its 95% confidence interval (95% CI) associated with perinatal factors. This hazard ratio (HR) and left truncation were used to adjust for the median lag of 7 months between diagnosis and interview. To account for the left truncation of survival times, women were

considered to be at risk of death from the time they were interviewed rather than from the time of diagnosis. Observations were censored on either the date of last known follow-up or the end date of the follow-up period. Based on a 10% change between crude and adjusted HRs, stage at diagnosis and birth order confounded the association between perinatal factors and mortality from breast cancer. For covariates that were missing a substantial percentage of data, we created a missing category for multivariate analyses. There was no evidence of confounding by family history of breast cancer, race, smoking, alcohol use, parity, recency of last birth before diagnosis, oral contraceptive use, exercise, education, income, or lactation. Nor was there evidence of confounding by variables that may be in the causal pathway between perinatal factors and breast cancer mortality, including age at menarche, body mass index, mammogram history, treatment history, birthweight, gestational age, twin birth, maternal smoking, or maternal hormone use. All analyses were initially adjusted for age of subject (continuous), diagnosis year (exact year), and stage at diagnosis (I, IIA, IIB, III+), and further adjusted for birth order (first, second, third+) or maternal age ( $<25$ , 25-29, 30-34, 35+ years). We stratified by stage at diagnosis, birth order, and maternal age, which are in the causal pathway between perinatal factors and breast cancer mortality, to determine the effect of perinatal factors on breast cancer mortality beyond their effect on intermediate variables. We assessed linear trend by treating categorical variables as continuous variables. Because birth order may modify the effect of maternal age on breast cancer mortality, we added an interaction term between maternal age ( $<30$  and 30+ years) and birth order (first and second+) to the proportional hazards model with the main effects and did the likelihood ratio test to examine whether there was evidence of effect modification. To determine whether the associations between perinatal factors and breast cancer mortality were mediated by treatment, we stratified by use of any adjuvant therapy, chemotherapy, radiation therapy, and hormone therapy.

## Results

Table 1 presents the HRs and 95% CIs for breast cancer mortality associated with perinatal factors. After adjustment for age at diagnosis, diagnosis year, and stage at diagnosis, women who were  $\geq 4,000$  g at birth had somewhat higher mortality from breast cancer relative to women whose birthweights were 2,500 to 3,999 g, which was more pronounced after further adjustment for birth order (HR, 1.8; 95% CI, 1.0-3.1). Before further adjustment for birth order, women whose mothers were of ages  $\geq 35$  years at their birth had somewhat lower mortality from breast cancer compared with women whose mothers were of ages  $<25$  years, which was reversed after further adjustment for birth order (HR, 1.7; 95% CI, 1.1-2.8). In addition, there was a trend of increasing mortality with increasing maternal age ( $P = 0.01$ ) evident after further adjustment for birth order. Women who were born second or higher in the birth order had substantially lower mortality from breast cancer (HR, 0.2; 95% CI, 0.2-0.3) and there was a trend of decreasing mortality with increasing birth order ( $P < 0.01$ ). Although based on very few cases, further adjustment for birth order resulted in higher mortality from breast cancer for being a twin (HR, 2.5; 95% CI, 1.0-6.2), which was not evident before adjustment for birth order. There was a slight reduction in mortality from breast cancer among women whose mothers used hormones during their pregnancy (HR, 0.6; 95% CI, 0.4-1.0).

Table 2 shows the joint effect of maternal age and birth order on mortality from breast cancer. The reference group is firstborn women whose mothers were of ages  $<30$  years at their birth. Birth order modified the effect of maternal age on

**Table 1. HRs of breast cancer mortality associated with perinatal factors**

|                      | Alive, N (%) | Dead, N (%) | HR* (95% CI)    | HR <sup>†</sup> (95% CI) |
|----------------------|--------------|-------------|-----------------|--------------------------|
| Birthweight (g)      |              |             |                 |                          |
| <2,500               | 63 (8.5)     | 12 (6.7)    | 0.9 (0.5-1.6)   | 0.9 (0.5-1.6)            |
| 2,500-3,999          | 632 (85.5)   | 153 (85.5)  | 1.0 (reference) | 1.0 (reference)          |
| 4,000+               | 44 (6.0)     | 14 (7.8)    | 1.5 (0.9-2.6)   | 1.8 (1.0-3.1)            |
| Missing              | 36           | 70          |                 |                          |
| <i>P</i> for trend   |              |             | 0.18            | 0.10                     |
| Maternal age (y)     |              |             |                 |                          |
| <25                  | 274 (36.0)   | 106 (43.3)  | 1.0 (reference) | 1.0 (reference)          |
| 25-29                | 238 (31.3)   | 68 (27.8)   | 0.9 (0.6-1.2)   | 1.2 (0.9-1.7)            |
| 30-34                | 156 (20.5)   | 46 (18.8)   | 0.8 (0.6-1.1)   | 1.4 (0.9-1.9)            |
| 35+                  | 93 (12.2)    | 25 (10.2)   | 0.8 (0.5-1.2)   | 1.7 (1.1-2.8)            |
| Missing              | 14           | 4           |                 |                          |
| <i>P</i> for trend   |              |             | 0.12            | 0.03                     |
| Birth order          |              |             |                 |                          |
| First                | 289 (37.3)   | 189 (75.9)  | 1.0 (reference) | 1.0 (reference)          |
| Second               | 234 (30.2)   | 25 (10.0)   | 0.2 (0.2-0.4)   | 0.2 (0.2-0.3)            |
| Third+               | 252 (32.5)   | 35 (14.1)   | 0.3 (0.2-0.4)   | 0.2 (0.2-0.3)            |
| <i>P</i> for trend   |              |             | <0.01           | <0.01                    |
| Gestational age (wk) |              |             |                 |                          |
| <37                  | 22 (3.4)     | 2 (2.4)     | 0.7 (0.2-2.7)   | 0.7 (0.2-2.7)            |
| 37-42                | 580 (89.4)   | 72 (87.8)   | 1.0 (reference) | 1.0 (reference)          |
| 43+                  | 47 (7.2)     | 8 (9.8)     | 1.4 (0.7-2.8)   | 1.4 (0.7-2.9)            |
| Missing              | 126          | 167         |                 |                          |
| <i>P</i> for trend   |              |             | 0.30            | 0.30                     |
| Twin birth           |              |             |                 |                          |
| No                   | 755 (98.8)   | 240 (98.0)  | 1.0 (reference) | 1.0 (reference)          |
| Yes                  | 9 (1.2)      | 5 (2.0)     | 1.6 (0.7-3.8)   | 2.5 (1.0-6.2)            |
| Missing              | 11           | 4           |                 |                          |
| Maternal smoking     |              |             |                 |                          |
| No                   | 230 (60.5)   | 107 (70.4)  | 1.0 (reference) | 1.0 (reference)          |
| Yes                  | 150 (39.5)   | 45 (29.6)   | 0.8 (0.5-1.1)   | 0.8 (0.5-1.1)            |
| Missing              | 395          | 97          |                 |                          |
| Maternal hormone use |              |             |                 |                          |
| No                   | 486 (64.0)   | 74 (74.0)   | 1.0 (reference) | 1.0 (reference)          |
| Yes                  | 273 (36.0)   | 26 (26.0)   | 0.6 (0.4-1.0)   | 0.6 (0.4-1.0)            |
| Missing              | 16           | 149         |                 |                          |

\*HR adjusted for age at diagnosis, diagnosis year, and stage at diagnosis.

<sup>†</sup>HR adjusted for age at diagnosis, diagnosis year, stage at diagnosis, and birth order, with exception of birth order, which is adjusted for maternal age.

mortality from breast cancer ( $P = 0.03$ ). The substantially reduced risk of mortality from breast cancer associated with higher birth order persisted regardless of maternal age. However, the increased risk of death from breast cancer among women whose mothers were older was seen among firstborn women only (HR, 1.6; 95% CI, 1.1-2.2). For all perinatal factors, our findings were similar among women who did and did not receive any adjuvant therapy, chemotherapy, radiation therapy, or hormone therapy (data not shown).

## Discussion

Although the Hertfordshire Cohort Study failed to find an association between birthweight and breast cancer mortality (12), we found a borderline increase in breast cancer mortality among women who were  $\geq 4,000$  g at birth relative to women whose birthweights were 2,500 to 3,999 g. We saw higher mortality from breast cancer among women whose mothers were of ages  $\geq 35$  years at their birth (HR, 1.7; 95% CI, 1.1-2.8) relative to women whose mothers were of ages  $< 25$  years at their birth. Although not significant, Holmberg et al. (13) reported an elevation in breast cancer mortality associated with a maternal age of  $\geq 45$  years (HR, 1.30; 95% CI, 0.85-1.98). We were unable to investigate advanced maternal age in our data because the mothers of only three women, all of whom survived, were of ages  $\geq 45$  years at their birth. Although the American Cancer Society Cancer Prevention Study 1 included women diagnosed pre- and postmenopausally, the majority of women were diagnosed after menopause (18). Both the Hertfordshire Cohort Study (12) and the American Cancer

Society Cancer Prevention Study 1 (13) included primarily women who were breast cancer free in the comparison group whereas our comparison group was women diagnosed with breast cancer, which may explain differences between their studies and the present study. Our most striking finding was the substantially lower mortality from breast cancer among women born second or higher in the birth order relative to firstborn women regardless of maternal age. In the present study, birth order modified the effect of maternal age on breast cancer mortality, with the higher breast cancer mortality associated with older maternal age seen among firstborn women only. To our knowledge, no other study has investigated the association between birth order and breast cancer mortality or its effect modification with maternal age.

In agreement with studies of perinatal factors and breast cancer incidence, we found higher mortality from breast

**Table 2. HRs of breast cancer mortality associated with joint effects of maternal age and birth order**

|                          |            | Alive, N (%) | Dead, N (%) | HR* (95% CI)    |
|--------------------------|------------|--------------|-------------|-----------------|
| Maternal age (y)         |            |              |             |                 |
| <30                      | Firstborn  | 242 (31.8)   | 137 (55.9)  | 1.0 (reference) |
|                          | Secondborn | 270 (35.5)   | 37 (15.1)   | 0.3 (0.2-0.4)   |
| 30+                      | Firstborn  | 37 (4.9)     | 48 (19.6)   | 1.6 (1.1-2.2)   |
|                          | Secondborn | 212 (27.9)   | 23 (9.4)    | 0.2 (0.2-0.4)   |
| Missing                  |            | 14           | 4           |                 |
| <i>P</i> for interaction |            |              |             | 0.03            |

\*HR adjusted for age at diagnosis, diagnosis year, and stage at diagnosis.

cancer for high birthweight (1); however, we also found higher mortality from breast cancer for older maternal age and lower mortality from breast cancer for higher birth order. The HR of 1.8 we found for birthweight of  $\geq 4,000$  g is close to the range of relative risks (1.5-1.7) reported in the review article (1), and is similar to the relative risk (1.7) we found in our previous study based on self-report (2). The HR of 1.7 we found for maternal age  $\geq 35$  years is higher than the relative risks for previous studies, which tended to report weak positive or no association (1), and is higher than the relative risk (1.0) we reported in our previous study (2). The HR of 0.2 we found for being second or higher in the birth order is lower than the relative risks of previous studies, which tended to report weak inverse or no association (1), and is lower than the relative risk (1.0) we reported in our previous study (2). Neither the review article nor our previous study accounted for effect modification, which has been seen in two (19, 20) of three (21) previous studies that investigated the joint effect of maternal age and birth order on breast cancer incidence.

If biological mechanisms proposed for the associations between perinatal factors and breast cancer incidence are similar for breast cancer mortality, a possible explanation for high birthweight is higher intrauterine exposure to insulin (7-9), insulin-like growth factor I (7-9), or leptin (9) based on cord blood levels. One (6) of two (5) studies that investigated cord estrogen levels found a positive association with older maternal age; thus, the Trichopoulos hypothesis (4) may hold for older maternal age and breast cancer mortality. An alternative explanation for higher breast cancer mortality associated with older maternal age is the greater likelihood of germ-cell mutations in the offspring (22) due to genetic damage of older oocytes (23) coupled with the inability of older mothers to repair DNA.<sup>4</sup> We did not assess older paternal age, which in a study of Hemminki and Kyyronen (22) resulted in a similar increase in sporadic breast cancer (10%) as that seen for older maternal age. Because cord estrogen levels were not associated with being firstborn (5, 6), an alternative explanation for lower breast cancer mortality associated with late rank in the birth order relates to the fetal antigen hypothesis whereby a pregnancy-induced immune response, initiated by fetal antigens produced by paternal genes during the first pregnancy, occurs between the mother and the fetus in subsequent pregnancies (24). The effect modification we saw of maternal age by birth order would support both of these hypotheses.

There were several limitations of this study. We were unable to assess maternal preeclampsia, history of having been breastfed, and paternal age. Data on some perinatal factors were missing for a substantial percentage of women, reducing statistical power to detect associations. Reporting of perinatal factors is prone to misclassification. We are confident that our loss of accuracy in using self-report rather maternal report was not that great because our validity study among women born in Washington state showed very high correlations comparing self-report with mother report for birth order ( $r = 0.89$ ) and birthweight ( $r = 0.85$ ; ref. 12). Proxy respondents were used for 172 deceased cases and few of these proxies were subjects' mothers. There was no validation of proxy reports and, to our knowledge, there have been no studies of proxy reporting of perinatal factors other than maternal reporting. For birthweight, we used a larger reference group of women (2,500-3,999 g) than the typical reference group (2,500-2,999 g) because we did not want to exclude women who were able to report that they were of low or high birthweight but did not know their exact birthweight.

This study has many strengths. This is the first study to investigate mortality from breast cancer associated with a range of perinatal factors. The population-based nature of the original study and its high response rates among living cases (82.4%) and proxies for deceased cases (81.9%) minimize selection bias. We evaluated effect modification of maternal age by birth order and assessed confounding by known risk factors for breast cancer mortality, including early screening and treatment. The mean and median length of follow-up of over 10 years should have been sufficient time to detect associations if they existed.

In all likelihood, these perinatal factors interact with genetic or environmental factors leading to a poorer prognosis for some women. The protective effect of being born second or higher in the birth order against breast cancer mortality is striking and needs to be confirmed in future studies.

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## ORIGINAL ARTICLE

## A case-control study of farming and prostate cancer in African-American and Caucasian men

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**Objective:** To determine the risk of prostate cancer associated with farming by duration, recency and specific activities among African-Americans and Caucasians.

**Methods:** This population-based case-control study had information on farming-related activities for 405 incident prostate cancer cases and 392 controls matched for age, race and region in South Carolina, USA, from 1999 to 2001. Cases with histologically confirmed, primary invasive prostate cancer who were aged between 65 and 79 years were ascertained through the South Carolina Central Cancer Registry. Appropriately matched controls were identified from the Health Care Financing Administration Medicare Beneficiary File. Data were collected using computer-assisted telephone interviewing, and adjusted odds ratios (aOR) were estimated using unconditional logistic regression.

**Results:** Farming was associated with increased risk of prostate cancer in Caucasians (aOR 1.8; 95% confidence interval (CI) 1.3 to 2.7) but not in African-Americans (aOR 1.0; 95% CI 0.6 to 1.6). Regarding specific farming activities, farmers who mixed or applied pesticides had a higher risk of prostate cancer (aOR 1.6; 95% CI 1.2 to 2.2). Increased risk of prostate cancer was observed only for those farming <5 years.

**Conclusions:** Increased risk of prostate cancer for farmers in this study may be attributable to pesticide exposure. Racial differences in the association between farming and prostate cancer may be explained by different farming activities or different gene-environment interactions by race.

Meta-analyses indicate that farming is more frequently associated with an increased risk of prostate cancer in North America than in other countries.<sup>1–3</sup> A total of 8 of 15 studies investigating incidence of prostate cancer in North America found a modestly increased risk among farmers compared with non-farmers, with effect estimates ranging from 1.1 to 4.3,<sup>4–11</sup> whereas 7 studies reported no association.<sup>12–18</sup> Interestingly, Krstev *et al.*<sup>9</sup> found a decreased risk for prostate cancer in farm workers, but an increased risk in those working in agricultural production or with livestock. Studies of mortality from prostate cancer in North America suggest an increase in mortality from prostate cancer among farmers compared with other occupations in 12 of 23 studies, ranging from 1.1 to 1.6.<sup>19–30</sup>

Some investigations have assessed prostate cancer risks associated with duration of farming or types of farming (crop, livestock and hay farming, and licensed pesticide application).<sup>5 6 8–10 12 13 16 26 31–33</sup> However, only one study assessed prostate cancer risk by farming duration and type of farming among African-Americans.<sup>9</sup> Although African-Americans have the highest incidence of prostate cancer in the world,<sup>34</sup> most studies that have evaluated the association between farming and prostate cancer have been carried out on Caucasian men. By contrast, only five studies have reported this association in non-white men<sup>24 28 29 35 36</sup> with an even fewer number of investigations in African-American men.<sup>9 25</sup> Two of these studies had <100 exposed cases in one or both of the racial categories, and one additional study failed to report the number of non-white cases in farmers. Therefore, we carried out a population-based case-control study to investigate the risk of prostate cancer among both African-American and Caucasian farmers using more refined measures of exposure (duration, recency of farming and specific farming-related activities) while controlling for potential confounders.

## METHODS

## Study population

The methods of data collection have been reported previously.<sup>37</sup> This population-based case-control study included cases with histologically confirmed, primary invasive prostate cancer who were residents of South Carolina, USA, aged between 65 and 79 years and ascertained through the South Carolina Central Cancer Registry (SCCCR) between 1999 and 2001. Of the 964 cases of prostate cancer reported to the SCCCR during the study period, attempts were made to include all 168 men with advanced disease (stages III and IV) and a random sample of cases with localised disease (stages I and II). African-American men were over sampled from those with localised disease (42% of Caucasian and 82% of African-American cases). Selected cases were contacted after obtaining permission from the diagnosing doctor. From 692 selected cases, 425 (61.4%) completed the interview; 90 (13.0%) doctors refused, 71 (10.3%) patients refused, 24 (3.5%) patients died before the interview, 59 (8.5%) were not located and 23 (3.3%) were too sick to participate. In all, 7 cases with prevalent prostate cancer were excluded from the case group, and 13 cases who did not provide complete interview data including farming-related exposures were excluded leaving 405 cases for analyses.

Controls were identified from the Health Care Financing Administration (HCFA) Medicare Beneficiary File and were eligible for participation if they were residents of South Carolina, USA, and aged between 65 and 79 years. 96% of South Carolina residents aged 65–79 years are included in the HCFA Beneficiary Files (according to the South Carolina Lieutenant Governor's Office on Aging). A total of 482 controls,

**Abbreviations:** aOR, adjusted odds ratio; BMI, body mass index; BPH, benign prostatic hyperplasia; CI, confidence interval; DRE, digital rectal examination; HCFA, Health Care Financing Administration; OR, odds ratio; PSA, prostate-specific antigen; REF, reference; SCCR, South Carolina Central Cancer Registry.

**Table 1** Comparison of cases and controls for demographic and lifestyle factors

|                                         | Cases (n = 405),<br>n (%) | Controls (n = 392),<br>n (%) |
|-----------------------------------------|---------------------------|------------------------------|
| Age (years)                             |                           |                              |
| 65–69                                   | 188 (46.4)                | 170 (43.4)                   |
| 70–74                                   | 130 (32.1)                | 114 (29.1)                   |
| 75–79                                   | 87 (21.5)                 | 108 (27.6)                   |
| Data missing                            | 0                         | 0                            |
| Race                                    |                           |                              |
| African-American                        | 166 (41.0)                | 167 (42.6)                   |
| Caucasian                               | 239 (59.0)                | 225 (57.4)                   |
| Data missing                            | 0                         | 0                            |
| Region                                  |                           |                              |
| Low country                             | 228 (56.3)                | 220 (56.1)                   |
| Midlands                                | 104 (25.7)                | 86 (21.9)                    |
| Upstate                                 | 73 (18.0)                 | 86 (21.9)                    |
| Data missing                            | 0                         | 0                            |
| Education                               |                           |                              |
| < 8th grade                             | 102 (25.4)                | 84 (21.4)                    |
| Grades 9–11                             | 53 (13.2)                 | 64 (16.3)                    |
| High-school graduate                    | 98 (24.4)                 | 90 (23.0)                    |
| Some college/technical school           | 53 (13.2)                 | 70 (17.9)                    |
| College graduate                        | 95 (23.7)                 | 84 (21.4)                    |
| p Value for trend                       | 0.39                      |                              |
| Data missing                            | 4                         | 0                            |
| BMI(kg/m <sup>2</sup> )                 |                           |                              |
| <24.4                                   | 90 (22.8)                 | 90 (23.6)                    |
| 24.4–27.2                               | 114 (28.9)                | 100 (26.2)                   |
| 27.3–29.8                               | 96 (24.3)                 | 96 (25.1)                    |
| ≥29.9                                   | 95 (24.1)                 | 96 (25.1)                    |
| p Value for trend                       | 0.67                      |                              |
| Data missing                            | 10                        | 10                           |
| Family history                          |                           |                              |
| No                                      | 277 (69.8)                | 328 (84.5)                   |
| Yes                                     | 120 (30.2)                | 60 (15.5)                    |
| Data missing                            | 8                         | 4                            |
| History of BPH                          |                           |                              |
| No                                      | 239 (59.9)                | 287 (73.8)                   |
| Yes                                     | 160 (40.1)                | 102 (26.2)                   |
| Data missing                            | 6                         | 3                            |
| Number of PSA tests in the past 5 years |                           |                              |
| 0                                       | 59 (14.6)                 | 85 (21.7)                    |
| 1–2                                     | 127 (31.4)                | 142 (36.3)                   |
| 3–4                                     | 64 (15.8)                 | 64 (16.4)                    |
| ≥5                                      | 155 (38.3)                | 100 (25.6)                   |
| p Value for trend                       | <0.001                    |                              |
| Data missing                            | 0                         | 1                            |
| Number of DRE tests in the past 5 years |                           |                              |
| 0                                       | 46 (11.4)                 | 48 (12.3)                    |
| 1–2                                     | 81 (20.0)                 | 107 (27.4)                   |
| 3–4                                     | 75 (18.5)                 | 81 (20.7)                    |
| ≥5                                      | 203 (50.1)                | 155 (39.6)                   |
| p Value for trend                       | 0.02                      |                              |
| Data missing                            | 0                         | 1                            |

BMI, body mass index; BPH, benign prostatic hyperplasia; DRE, digital rectal examination; PSA, prostate specific antigen.

frequency matched to cases for age, race and geographical region, were randomly selected from the beneficiary file. The participation rate among the controls was 63.8%. Of the remaining eligible controls, 108 (14.3%) refused, 22 (2.9%) died before the interview, 112 (14.8%) were not located and 32 (4.2%) were too sick to participate. A total of 52 cases with prevalent prostate cancer were identified through medical chart review and excluded from the control group. After eliminating the 52 controls with prevalent prostate cancer and 38 controls whose interviews were incomplete, 392 controls remained for analyses.

### Farming exposures

Participants were interviewed by telephone using computer-assisted technology. Information collected included demographics, alcohol and tobacco use, medical history and

farm-related exposures. Participants were dichotomously classified as farmers using the question, “Since you were 14 years old, have you ever worked on a farm?”. Specific farming activities, exposure to pesticides, duration and recency of farming were evaluated for the farmers. Duration of farming was assessed using the question, “After age 14, how many years have you farmed or worked on a farm?”. Non-farmers were the referent group and were compared with those farming for 0–4 years, 5–9 years, 10–20 years or 21–65 years. Recency of farming was classified using last year of farming and obtained with the question, “In what year did you last work on a farm?”. Those who last farmed before 1950, from 1950 to 1959, from 1960 to 1979 and from 1980 to 2001 were compared with non-farmers. Farming activities were assessed using the question, “During the time you worked on a farm, did you do any of the following activities?”. Responses to the questions regarding 17 farming activities were evaluated to identify activities that all farmers carried out (eg, planting crops, tilling soil, harvesting crops), as well as activities that consistently co-occurred. Similar activities were combined to yield six activity groups: handled hay/grain/silage, harvested tobacco, planted/picked crops or tilled soil, picked cotton, repaired pesticide equipment, or fed animals/worked with poultry or swine. Indicator variables were created to compare (a) farmers who reported the activity (exposed farmers) and (b) farmers not reporting the activity (unexposed farmers) with (c) non-farmers. In addition, pesticide use among farmers was assessed with the question, “Have you personally mixed or applied any of the following: herbicides, insecticides, fumigants, or fungicides?”. In a similar manner, three groups were created to compare (a) farmers exposed to pesticides and (b) farmers not exposed to pesticides with (c) non-farmers.

Information about education, body mass index, family history of prostate cancer, benign prostatic hyperplasia (BPH), prostate cancer screening behaviour (prostate-specific antigen (PSA) and digital rectal examination (DRE)), drinking, smoking, leisure-time physical activity and dietary factors was ascertained by a questionnaire<sup>37</sup> and each factor was evaluated as a potential confounder. Body mass index, smoking duration (in years), drinking duration (in years) and dietary factors (consumption of animal fat, fruits and vegetables, and dairy products) were treated categorically on the basis of quartiles of the distribution in the controls. Family history and BPH were treated as dichotomous variables. The PSA and DRE variables were categorised by the number of tests in the past 5 years (0, 1–2, 3–4, ≥5).

### Statistical analysis

Unconditional logistic regression was used to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CI) for farming exposures for all men, and separately by race. None of the potential risk factors that were tested met the 10% change between crude and adjusted point estimates criteria for confounding, hence ORs were adjusted only for the three matching variables (age, race and South Carolina region). Effect modification was evaluated using the likelihood ratio test with a p value of 0.05.

### Ethics approval

This study received institutional review board approval from the University of South Carolina, South Carolina, USA, Centers for Disease Control and Prevention and National Cancer Institute.

### RESULTS

The 405 cases and 392 controls included in this analysis were similar with respect to age, race and region (table 1), indicating

**Table 2** Farming exposures and risk of prostate cancer

| Exposure measure                      | Cases,<br>n = 405 (%) | Controls,<br>n = 392 (%) | OR* | 95% CI     |
|---------------------------------------|-----------------------|--------------------------|-----|------------|
| Farming                               |                       |                          |     |            |
| Non-farmers                           | 181 (44.7)            | 205 (52.3)               | 1   | Ref        |
| Ever farmed                           | 224 (55.3)            | 187 (47.7)               | 1.4 | 1.1 to 1.9 |
| Data missing                          | 0                     | 0                        |     |            |
| Years of farming                      |                       |                          |     |            |
| Non-farmers                           | 181 (45.8)            | 205 (53.7)               | 1   | Ref        |
| Farmers                               |                       |                          |     |            |
| ≤4                                    | 100 (25.3)            | 75 (19.6)                | 1.5 | 1.1 to 2.2 |
| 5–9                                   | 47 (11.9)             | 40 (10.5)                | 1.4 | 0.9 to 2.3 |
| 10–20                                 | 33 (8.4)              | 26 (6.8)                 | 1.5 | 0.9 to 2.7 |
| 21–65                                 | 34 (8.6)              | 36 (9.4)                 | 1.1 | 0.7 to 1.9 |
| p Value for trend                     | 0.51                  |                          |     |            |
| Data missing                          | 10                    | 10                       |     |            |
| Recency of last farming               |                       |                          |     |            |
| Non-farmers                           | 181 (48.8)            | 205 (58.2)               | 1   | Ref        |
| Farmers                               |                       |                          |     |            |
| Before 1950                           | 64 (17.3)             | 34 (9.7)                 | 2.1 | 1.3 to 3.4 |
| 1950–9                                | 90 (24.3)             | 73 (20.7)                | 1.5 | 1.0 to 2.2 |
| 1960–79                               | 21 (5.7)              | 18 (5.1)                 | 1.3 | 0.7 to 2.6 |
| 1980+                                 | 15 (4.0)              | 22 (6.3)                 | 0.8 | 0.4 to 1.6 |
| p Value for trend                     | 0.02                  |                          |     |            |
| Data missing                          | 34                    | 40                       |     |            |
| Mixed/applied pesticides              |                       |                          |     |            |
| Non-farmers                           | 181 (44.8)            | 205 (52.4)               | 1   | Ref        |
| Farmers                               |                       |                          |     |            |
| Never mixed                           | 46 (11.4)             | 56 (14.3)                | 1   | 0.6 to 1.5 |
| Ever mixed                            | 177 (43.8)            | 130 (33.3)               | 1.6 | 1.2 to 2.2 |
| Data missing                          | 1                     | 1                        |     |            |
| Handle hay, grain, silage             |                       |                          |     |            |
| Non-farmers                           | 181 (44.8)            | 205 (52.3)               | 1   | Ref        |
| Farmers                               |                       |                          |     |            |
| Never handled                         | 22 (5.5)              | 18 (4.6)                 | 1.4 | 0.7 to 2.7 |
| Ever handled                          | 201 (49.8)            | 169 (43.1)               | 1.4 | 1.1 to 1.9 |
| Data missing                          | 1                     | 0                        |     |            |
| Harvest tobacco                       |                       |                          |     |            |
| Non-farmers                           | 181 (44.8)            | 205 (52.3)               | 1   | Ref        |
| Farmers                               |                       |                          |     |            |
| Never harvested                       | 136 (33.7)            | 114 (29.1)               | 1.4 | 1.0 to 2   |
| Ever harvested                        | 87 (21.5)             | 73 (18.6)                | 1.4 | 0.9 to 2   |
| Data missing                          | 1                     | 0                        |     |            |
| Plant/pick crops, till soil           |                       |                          |     |            |
| Non-farmers                           | 181 (44.7)            | 205 (52.3)               | 1   | Ref        |
| Farmers                               |                       |                          |     |            |
| Never planted                         | 10 (2.5)              | 8 (2.0)                  | 1.4 | 0.5 to 3.6 |
| Ever planted                          | 214 (52.8)            | 179 (45.7)               | 1.4 | 1.1 to 1.9 |
| Data missing                          | 0                     | 0                        |     |            |
| Pick cotton                           |                       |                          |     |            |
| Non-farmers                           | 181 (44.7)            | 205 (52.3)               | 1   | Ref        |
| Farmers                               |                       |                          |     |            |
| Never picked                          | 86 (21.2)             | 45 (11.5)                | 2.1 | 1.4 to 3.3 |
| Ever picked                           | 138 (34.1)            | 142 (36.2)               | 1.1 | 0.8 to 1.6 |
| Data missing                          | 0                     | 0                        |     |            |
| Repair pesticide equipment            |                       |                          |     |            |
| Non-farmers                           | 181 (44.8)            | 205 (52.3)               | 1   | Ref        |
| Farmers                               |                       |                          |     |            |
| Never repaired                        | 172 (42.6)            | 141 (36.0)               | 1.5 | 1.1 to 2   |
| Ever repaired                         | 51 (12.6)             | 46 (11.7)                | 1.3 | 0.8 to 2   |
| Data missing                          | 1                     | 0                        |     |            |
| Feed animals, work with poultry/swine |                       |                          |     |            |
| Non-farmers                           | 181 (44.8)            | 205 (52.3)               | 1   | Ref        |
| Farmers                               |                       |                          |     |            |
| Never fed                             | 23 (5.7)              | 17 (4.3)                 | 1.6 | 0.8 to 3.1 |
| Ever fed                              | 200 (49.5)            | 170 (43.4)               | 1.4 | 1.0 to 1.9 |
| Data missing                          | 1                     | 0                        |     |            |

ref, reference.

\*Adjusted for age, race and region.

effective frequency matching in the design phase. Cases were more likely than controls to report a family history of prostate cancer, a history of BPH and greater frequency of PSA and DRE in the past 5 years.

Table 2 presents aOR and 95% CI for various measures of farming exposures and prostate cancer. Men who reported ever working as farmers had an increased risk of prostate cancer

compared with those who had never farmed (aOR 1.4; 95% CI 1.1 to 1.9). When considering the duration of farming, only those farming for a short period (0–4 years) had an increased risk of prostate cancer compared with non-farmers. Furthermore among farmers there was no dose–response relationship between increasing years of farming and risk of prostate cancer (p value for trend 0.51). Regarding the recency of farming, only men who last farmed before 1960 had an increased risk of prostate cancer compared with non-farmers. Regarding specific farming activities, mixing or applying pesticides (aOR 1.6; 95% CI 1.2 to 2.2) and not picking cotton (aOR 2.1; 95% CI 1.4 to 3.3) were associated with an increased risk of prostate cancer compared with non-farmers.

Table 3 presents the risk of prostate cancer associated with farming by race. Race modified the association between farming and prostate cancer (Breslow–Day  $\chi^2$  p value for interaction = 0.04). Farming was associated with prostate cancer among Caucasians (aOR 1.8; 95% CI 1.3 to 2.7) but not among African-Americans (aOR 1.0; 95% CI 0.6 to 1.6). As was observed among all men, farming for shorter duration (<10 years) and year last farmed occurring before 1960 were associated with prostate cancer risk, but only for Caucasian men. Mixing or applying pesticides was associated with an increased prostate cancer risk only for Caucasian men (p value for interaction = 0.11 by race for pesticide use and prostate cancer risk). For both Caucasian and African-American men, never picking cotton was associated with an increased prostate cancer risk that was more pronounced among African-American than among Caucasian men (p value for interaction = 0.08).

## DISCUSSION

Our finding that farming was associated with a modest increase in prostate cancer risk is consistent with other studies conducted in the USA and Canada. We did not find any dose–response relationship between increasing years of farming and prostate cancer risk, which is also consistent with the existing literature.<sup>12–13</sup> Furthermore, our finding of an increased risk of prostate cancer among individuals who farmed for the shortest duration (≤4 years) was consistent with prior studies with incidence<sup>9</sup> or mortality<sup>26</sup> from prostate cancer as the outcome. As suggested in the literature, short-term workers in general may be exposed to higher levels of contaminants or may differ from long-term workers in lifestyle and health-related factors.<sup>38</sup> Among farmers, short-term workers are more likely to be manual labourers, whereas those who participate in farming for longer periods are more likely to be farm owners and managers. Farm labourers may have higher or more direct exposure to pesticides than farm owners.<sup>3–39</sup> To restrict the window of exposure to include only those years of farming likely to be aetiologically relevant to prostate cancer, we repeated our analyses on duration of farming and excluded years farmed within (a) 5 and (b) 10 years of case diagnosis for cases and in (1) 5 and (2) 10 years of the year 2000 for controls. Adjusted odds ratios remained insignificant in all cases.

We found an inverse trend between the recency of last year farmed and risk of prostate cancer with a significantly increased OR for those farming before 1960. One explanation for this finding may be that exposures to pesticides and other contaminants may have varied in time on the basis of pesticides used, pesticide application methods, pesticide regulations, crop planting and harvesting methods, and personal protective equipment availability and use.<sup>1</sup> Another possible explanation is that a greater percentage (58%) of those who farmed before 1960 farmed for ≤4 years, whereas 56% of those farming after 1960 farmed for >21 years.

**Table 3** Farming and risk of prostate cancer by race

| Exposure measure                      | Caucasians     |                   |                  | African-Americans |                   |               |
|---------------------------------------|----------------|-------------------|------------------|-------------------|-------------------|---------------|
|                                       | Cases, n = 239 | Controls, n = 225 | OR* (95% CI)     | Cases, n = 166    | Controls, n = 167 | OR* (95% CI)  |
| Farming                               |                |                   |                  |                   |                   |               |
| Never farmed                          | 122 (51.1)     | 147 (65.3)        | 1 Ref            | 59 (35.5)         | 58 (34.7)         | 1 Ref         |
| Ever farmed                           | 117 (49.0)     | 78 (34.7)         | 1.8 (1.3 to 2.7) | 107 (64.5)        | 109 (65.3)        | 1 (0.6–1.6)   |
| Data missing                          | 0              | 0                 |                  | 0                 | 0                 |               |
| Years of farming                      |                |                   |                  |                   |                   |               |
| Non-farmers                           | 122 (51.5)     | 147 (65.9)        | 1 Ref            | 59 (37.3)         | 58 (36.5)         | 1 Ref         |
| Farmers                               |                |                   |                  |                   |                   |               |
| ≤ 4                                   | 63 (26.6)      | 40 (17.9)         | 1.9 (1.2 to 3)   | 37 (23.4)         | 35 (22.0)         | 1.1 (0.6–1.9) |
| 5–9                                   | 24 (10.1)      | 14 (6.3)          | 2.1 (1.1 to 4.3) | 23 (14.6)         | 26 (16.4)         | 0.9 (0.5–1.8) |
| 10–20                                 | 13 (5.5)       | 9 (4.0)           | 1.8 (0.7 to 4.3) | 20 (12.7)         | 17 (10.7)         | 1.2 (0.6–2.6) |
| 21–65                                 | 15 (6.3)       | 13 (5.8)          | 1.4 (0.6–3.1)    | 19 (12.0)         | 23 (14.5)         | 0.8 (0.4–1.7) |
| p Value for trend                     | 0.53           |                   |                  | 0.84              |                   |               |
| Data missing                          | 2              | 2                 |                  | 8                 | 8                 |               |
| Recency of last farming               |                |                   |                  |                   |                   |               |
| Non-farmers                           | 122 (55.0)     | 147 (69.7)        | 1 Ref            | 59 (39.6)         | 58 (41.1)         | 1 Ref         |
| Farmers                               |                |                   |                  |                   |                   |               |
| Before 1950                           | 32 (14.4)      | 13 (6.2)          | 2.9 (1.4 to 5.8) | 32 (21.5)         | 21 (14.9)         | 1.5 (0.8–2.9) |
| 1950–9                                | 54 (24.3)      | 37 (17.5)         | 1.8 (1.1 to 3)   | 36 (24.2)         | 36 (25.5)         | 1.1 (0.6–2.1) |
| 1960–79                               | 8 (3.6)        | 5 (2.4)           | 1.9 (0.6 to 6.1) | 13 (8.7)          | 13 (9.2)          | 0.9 (0.4–2.1) |
| 1980+                                 | 6 (2.7)        | 9 (4.3)           | 0.8 (0.3 to 2.3) | 9 (6.0)           | 13 (9.2)          | 0.7 (0.3–1.8) |
| p Value for trend                     | 0.05           |                   |                  | 0.14              |                   |               |
| Data missing                          | 17             | 14                |                  | 17                | 26                |               |
| Mixed/applied pesticides              |                |                   |                  |                   |                   |               |
| Non-farmers                           | 122 (51.3)     | 147 (65.3)        | 1 Ref            | 59 (35.5)         | 58 (34.9)         | 1 Ref         |
| Farmers                               |                |                   |                  |                   |                   |               |
| Never mixed                           | 20 (8.4)       | 14 (6.2)          | 1.7 (0.8 to 3.5) | 26 (15.7)         | 42 (25.3)         | 0.6 (0.3–1.2) |
| Ever mixed                            | 96 (40.3)      | 64 (28.4)         | 1.8 (1.2 to 2.7) | 81 (48.8)         | 66 (39.8)         | 1.2 (0.8–2.0) |
| Data missing                          | 1              | 0                 |                  | 0                 | 1                 |               |
| Handle hay, grain, silage             |                |                   |                  |                   |                   |               |
| Non-farmers                           | 122 (51.3)     | 147 (65.3)        | 1 Ref            | 59 (35.5)         | 58 (34.7)         | 1.0 Ref       |
| Farmers                               |                |                   |                  |                   |                   |               |
| Never handled                         | 14 (5.9)       | 6 (2.7)           | 2.7 (1.0 to 7.2) | 8 (4.8)           | 12 (7.2)          | 0.7 (0.3–1.8) |
| Ever handled                          | 102 (42.9)     | 72 (32.0)         | 1.7 (1.2 to 2.6) | 99 (59.6)         | 97 (58.1)         | 1.0 (0.7–1.7) |
| Data missing                          | 1              | 0                 |                  | 0                 | 0                 |               |
| Harvest tobacco                       |                |                   |                  |                   |                   |               |
| Non-farmers                           | 122 (51.3)     | 147 (65.3)        | 1 Ref            | 59 (35.5)         | 58 (34.7)         | 1 Ref         |
| Farmers                               |                |                   |                  |                   |                   |               |
| Never harvested                       | 79 (33.2)      | 53 (23.6)         | 1.8 (1.2 to 2.8) | 57 (34.3)         | 61 (36.5)         | 1 (0.6–1.7)   |
| Ever harvested                        | 37 (15.6)      | 25 (11.1)         | 1.8 (1.0 to 3.1) | 50 (30.1)         | 48 (28.7)         | 1 (0.6–1.8)   |
| Data missing                          | 1              | 0                 |                  | 0                 | 0                 |               |
| Plant/pick crops, till soil           |                |                   |                  |                   |                   |               |
| Non-farmers                           | 122 (51.1)     | 147 (65.3)        | 1 Ref            | 59 (35.5)         | 58 (34.7)         | 1 Ref         |
| Farmers                               |                |                   |                  |                   |                   |               |
| Never planted                         | 7 (2.9)        | 6 (2.7)           | 1.4 (0.4 to 4.2) | 3 (1.8)           | 2 (1.2)           | 1.6 (0.2–9.9) |
| Ever planted                          | 110 (46.0)     | 72 (32.0)         | 1.9 (1.3 to 2.8) | 104 (62.7)        | 107 (64.1)        | 1 (0.6–1.6)   |
| Data missing                          | 0              | 0                 |                  | 0                 | 0                 |               |
| Pick cotton                           |                |                   |                  |                   |                   |               |
| Non-farmers                           | 122 (51.1)     | 147 (65.3)        | 1 Ref            | 59 (35.5)         | 58 (34.7)         | 1 Ref         |
| Farmers                               |                |                   |                  |                   |                   |               |
| Never picked                          | 65 (27.2)      | 38 (16.9)         | 2.1 (1.3 to 3.3) | 21 (12.7)         | 7 (4.2)           | 2.9 (1.1–7.3) |
| Ever picked                           | 52 (21.8)      | 40 (17.8)         | 1.6 (1.0 to 2.6) | 86 (51.8)         | 102 (61.1)        | 0.8 (0.5–1.4) |
| Data missing                          | 0              | 0                 |                  | 0                 | 0                 |               |
| Repair pesticide equipment            |                |                   |                  |                   |                   |               |
| Non-farmers                           | 122 (51.3)     | 147 (65.3)        | 1 Ref            | 59 (35.5)         | 58 (34.7)         | 1 Ref         |
| Farmers                               |                |                   |                  |                   |                   |               |
| Never repaired                        | 88 (37.0)      | 58 (25.8)         | 1.9 (1.2 to 2.8) | 84 (50.6)         | 83 (49.7)         | 1 (0.6–1.7)   |
| Ever repaired                         | 28 (11.8)      | 20 (8.9)          | 1.7 (0.9 to 3.1) | 23 (13.9)         | 26 (15.6)         | 0.9 (0.4–1.7) |
| Data missing                          | 1              | 0                 |                  | 0                 | 0                 |               |
| Feed animals, work with poultry/swine |                |                   |                  |                   |                   |               |
| Non-farmers                           | 122 (51.3)     | 147 (65.3)        | 1 Ref            | 59 (35.5)         | 58 (34.7)         | 1 Ref         |
| Farmers                               |                |                   |                  |                   |                   |               |
| Never fed                             | 13 (5.5)       | 7 (3.1)           | 2.4 (0.9 to 6.1) | 10 (6.0)          | 10 (6.0)          | 1 (0.4–2.6)   |
| Ever fed                              | 103 (43.3)     | 71 (31.6)         | 1.8 (1.2 to 2.6) | 97 (58.4)         | 99 (59.3)         | 1 (0.6–1.6)   |
| Data missing                          | 1              | 0                 |                  | 0                 | 0                 |               |

Ref, Reference.

\*Adjusted for age and region.

Mixing or applying pesticides was strongly associated with the risk of prostate cancer in our data. This is similar to findings reported by Fleming *et al*<sup>26</sup> of twice the expected incidence and 2.5 times the expected mortality from prostate cancer in agricultural pesticide applicators compared with the general Florida population. Alavanja *et al*,<sup>4</sup> also reported an excess in

the incidence of prostate cancer among agricultural pesticide applicators compared with the general North Carolina and Iowa populations. A recent meta-analysis of prostate cancer among pesticide applicators by Van Maele-Fabry *et al*<sup>2</sup> reported a small but marked increase in the risk of prostate cancer among pesticide applicators. Taken together, these studies suggest that

exposure to pesticides may play an important role in increasing prostate cancer risk, and that protective gear should be worn when mixing or applying pesticides.

As a class of agents, pesticide exposure provides a biologically plausible link between farming and increased risk of prostate cancer. Keller-Byrne *et al*<sup>40</sup> in their meta-analysis of prostate cancer and farming provide support for this association on the basis of their review of toxicological studies of pesticide binding to steroid hormone receptors, which then induces proliferation of prostate cancer cells. A later review of environmental endocrine modulators (including pesticides) and human health effects<sup>41</sup> proposed a number of mechanisms of action that disrupt the endocrine system, including interactions of chemicals with endogenous hormones or their carrier proteins to prevent receptor binding. The mechanism through which pesticide exposure may lead to prostate cancer is complex, probably differs by pesticide, and deserves attention in future research.

Our finding of an increased risk of prostate cancer among farmers who never picked cotton is difficult to explain, although those who never picked cotton were more likely to have farmed for shorter durations, and this group of farmers had the highest prostate cancer risk. Thus, the observed increased risk associated with never picking cotton may be related to a shorter duration of farming and only spuriously associated with not picking cotton. Further, among Caucasian men only, both picking and not picking cotton were associated with prostate cancer risk, indicating that this activity is not probably aetiologically linked with prostate cancer. Many of the remaining farming activities were common in all farmers (eg 86% of farmers handled hay, grain or silage, 96% planted or pick crops, or tilled soil; and 90% fed animals, worked with poultry or swine), and thus the power to consider these activities and prostate cancer risk was limited.

Our finding of an interaction between race and farming on risk of prostate cancer is consistent with the only other study<sup>9</sup> to deal with prostate cancer risk in African-American and Caucasian men. Krstev *et al*<sup>9</sup> also found that farming was associated with an increased risk of prostate cancer among Caucasians but not among African-American men. Heterogeneity of effects by race could be explained by different distributions of genetic factors by race and interactions between these genetic factors and environmental exposures.

This study is not without limitations. As 96% of South Carolina residents aged 65–79 years are included in the HCFA Beneficiary Files and as we have a nearly complete sampling frame for the population that would have given rise to the cases, this can be considered a population-based sample, which limits the potential for selection bias. However, the response rate was only fair among cases and controls (61.4% and 63.8%, respectively), and we were unable to locate a larger proportion of African-Americans (19.3%) compared with Caucasians (6.0%). Selection bias may be introduced with lower response rates. Among participants with correct contact information, we were able to interview 76.4% (78.3% of cases and 74.8% of controls) of potential participants. We identified and excluded prevalent cases in both the controls and the cases using medical chart reviews to reduce outcome misclassification. To reduce exposure misclassification, we used computer-assisted telephone interviewing rather than self-administered questionnaires or information about occupation collected only from cancer registries or death certificates. Nonetheless, there was potential for recall bias in reporting attributes of farming exposure. Cases and controls may differentially remember or report their farming-related exposures. Typically, cases have an incentive to more carefully recall exposures than controls. If this pattern holds in this case-control study, recall bias would

## Main messages

- Farming-related exposures were associated with an increased risk of prostate cancer among Caucasians but not among African-Americans.
- Prostate cancer risk was highest for those farming for shorter periods and for those who mixed or applied pesticides.
- Exposure to pesticides may play a role in increasing the risk of prostate cancer among farmers.

## Policy implications

- Prostate cancer is the most common cancer in men, yet the aetiology remains unclear.
- Consistent use of protective gear when applying pesticides is strongly recommended to minimise the effect of pesticide exposure that may be associated with the risk of prostate cancer.
- Future studies should develop and apply exposure assessments that incorporate information about the intensity, frequency and duration of exposure to specific pesticides in studies evaluating the risk of prostate cancer among agricultural workers.
- Race should be considered as an effect modifier in future studies on prostate cancer and farming.

be expected to bias the resulting OR away from the null. However, if recall bias were truly observed in these data, we would expect a bias away from the null for both Caucasian and African-American men, whereas we observed an increased risk only among Caucasian men. Although we had sufficient numbers to investigate farming activities for the entire study population, we had limited study power to investigate some specific farming activities by race. As we did not collect information on whether farmers were farm workers or owners, we could not examine differences in years of farming by type of farming. Information on farming type may have provided support for the theory that short-term farmers are more likely to be farm labourers rather than farm owners.

Although a number of associations between specific activities (which represent crude surrogates of pesticide exposure) and increased prostate cancer risk were evaluated, issues of multiple comparisons may have arisen. Nonetheless, an interesting finding relates to the pattern of differences in the strength of the association between Caucasians and African-Americans for many of the farm activity–prostate cancer risk associations that were evaluated. As the associations between farming and prostate cancer were typically stronger among Caucasians compared with African-Americans, this general finding may inform future studies to consider race as an effect modifier of the farming–prostate cancer association.

Our study adds to the existing literature by investigating the risk of prostate cancer associated with years of farming, recency of farming, and specific farming activities, stratified by race, which have not been reported previously in the literature. Although most specific farming-related exposures were not associated with prostate cancer, farmers who mixed or applied pesticides were at increased risk of prostate cancer compared with non-farmers and farmers who never mixed or applied pesticides. It is biologically plausible that pesticide exposures may be aetiologically linked with an increased risk of prostate

cancer and other hormone-dependent cancers.<sup>40</sup> Further studies considering polymorphisms in genes that regulate the metabolism of pesticides or other chemicals common in farming-related work and prostate cancer risk would advance our understanding of the mechanism by which exposures experienced while engaged in farming-related activities may increase prostate cancer risk.

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**ORIGINAL ARTICLE****Serum Leptin Concentration, Adiposity, and Body Fat Distribution in Mexican-Americans**

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**Background.** Leptin is strongly associated with adiposity and few studies have investigated its role in Mexican-Americans. The aims of this study were to examine the association of serum leptin concentration with adiposity and body fat distribution in Mexican-Americans and to develop a predictive model of serum leptin concentration for this ethnic group.

**Methods.** Three hundred fifty-two college students (242 women, 110 men; age 18–30 years) were evaluated in this cross-sectional study. Body fat content was assessed using bioelectrical impedance analysis. Correlation between serum leptin levels and several markers of adiposity and body fat distribution were examined in both men and women. Multiple regression analysis was performed to create the predictive model.

**Results.** Women had higher serum leptin concentrations than men for the same levels of adiposity. After controlling for gender and body fat, only fat mass (FM) expressed in kg, was significantly correlated with serum leptin concentration in men (partial  $\rho = 0.811$ ,  $p < 0.001$ ), whereas body mass index (BMI), hip circumference (HC), and FM expressed in kg, were significantly correlated with serum leptin concentration in women (partial  $\rho = 0.214$ ,  $p < 0.001$ ; partial  $\rho = 0.201$ ,  $p < 0.01$ ; and partial  $\rho = 0.818$ ,  $p < 0.001$ , respectively). Percent body fat (PBF) was the only significant predictor of serum leptin concentration among men, explaining 42% of the variance in serum leptin concentration. In addition to PBF, waist circumference (WC) and HC were significant predictors of serum leptin concentration among women explaining 65% of the variance in serum leptin concentration.

**Conclusions.** Serum leptin concentration is a function of adiposity as determined by PBF in both Mexican-American men and women. HC and WC are associated with serum leptin concentration in Mexican-American women but not in men. BMI alone should not be used in evaluating the association of serum leptin concentration with body fatness in Mexican-Americans. © 2007 IMSS. Published by Elsevier Inc.

**Key Words:** Leptin, Adiposity, Body fat distribution, Mexican-Americans.

**Introduction**

The past decade has seen an important advance in the understanding of the regulation of energy balance and food intake, providing significant knowledge regarding the path-

ogenesis of obesity. Adipocyte-derived cytokines including leptin, adiponectin, adipisin, and resistin have been extensively investigated for their association with obesity, and very strong evidence exists that such cytokines play a critical role in regulating body weight (1–3). Leptin, a protein encoded by the *ob* gene (4), is produced by adipocytes and is secreted into the circulation (3). It regulates food intake and energy expenditure (3), binding mainly to receptors in the hypothalamus and influencing the expression of several

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neuropeptides (5). Free leptin, the form present in cerebrospinal fluid, has been shown to be the biologically active form of leptin (6). Evidence points out that leptin-binding proteins are saturated in states of increased adiposity (7). At high concentrations, leptin provides a negative feedback signal to the brain, which in turn reduces food intake and increases energy expenditure (5). However, elevated serum leptin levels have been reported in a large proportion of obese individuals, which implies resistance to endogenous leptin in human obesity (8,9). Leptin concentration in both plasma and cerebrospinal fluid is higher in women than in men, which raises the possibility that women are relatively leptin resistant (10). It has been suggested that the higher serum leptin concentration in women is, at least partially, the result of higher body fat content compared to men (11).

Serum and plasma leptin concentrations have been associated with body mass index (BMI) (8,12–15). However, BMI (measured as weight in kilograms divided by height in meters squared) takes into account body weight and body height instead of body fat content defined as the fat component of the body weight (16). Limited attention has been paid to the relationship of leptin concentrations with body composition measures other than BMI. Because BMI does not accurately measure adiposity, the effects of body fatness on leptin concentration may be more pronounced when more reliable methods such as bioelectrical impedance analysis (BIA), underwater weighing (UWW), dual-energy X-ray absorptiometry (DXA), computed tomography, and magnetic resonance imaging are used to measure total body fat content. In the few studies when adiposity was measured using such tools, the effect of adiposity on leptin concentration was more evident in both men and women (17–20). Among the accurate methods of body composition, BIA is the simplest, cheapest, fastest, and least invasive method suitable for clinical and field epidemiologic research. BIA has been validated as an indicator of adiposity against gold-standard methods such as UWW and DXA (21,22) and has been used in large multiethnic nationally representative surveys such as the National Health and Nutrition Examination Survey III (23).

Body fat distribution has been shown to play an important role in many metabolic disorders (24). Studies examining the association of leptin concentration with body fat distribution have shown conflicting results. Both subcutaneous (25–29) and visceral adipose tissue depots (30) have been associated with high serum leptin levels. The San Antonio Heart Study, a population-based cohort study of type-2 diabetes and cardiovascular disease, has found that serum leptin concentrations are associated with all adipose tissue depots and not disproportionately with upper body or central adiposity in a sample of 147 Mexican-Americans (31). In another study, serum leptin concentrations were not associated with waist circumference (WC) after adjustment for fat mass but were associated with hip circumference (HC) in women (32). Although waist/hip ratio (WHR) is the most

frequent marker of body fat distribution pattern (16), WC has been considered a surrogate for central obesity (33–35), whereas HC is a proxy measure of peripheral obesity (31,32,36). In summary, the relationship between serum leptin levels and body fat distribution in different ethnic groups remains unclear.

The objectives of this study were to determine the association of serum leptin concentration with (i) several anthropometric parameters including body fat content and (ii) body fat distribution in a large sample of Mexican-Americans. In addition, we sought to develop a predictive model of leptin concentration for Mexican Americans that could be used for clinical and epidemiological purposes.

## Materials and Methods

### Subjects

From September 2004 to December 2005, 359 Mexican-American college students (248 women and 111 men) attending the University of Texas at Brownsville & Texas Southmost College (UTB/TSC) volunteered to participate in this cross-sectional study. Seven participants were excluded due to extremely high values of serum leptin concentration ( $>200$  ng/mL) resulting in 242 women and 110 men for analysis. Recruitment activities such as classroom presentations and posting of flyers throughout campus were accomplished by research staff. Information on self-reported ancestry was used to define subjects as Mexican-Americans. Participants were enrolled if all four grandparents were of Mexican ancestry. Pregnancy was the sole criterion for exclusion of participants. The response rate was 90% among those who indicated they were interested in participating in the study. The study protocol was approved by the UTB/TSC Institutional Review Board and the University of Texas–Houston Health Science Center Committee for the Protection of Human Subjects. All participants were required to sign written informed consent before participating in the study. All anthropometric, bioelectrical impedance analysis and serum leptin concentration measurements were performed in duplicate during weekdays from 7:30 to 10:30 AM at the Student Health Services at UTB/TSC by trained research staff.

### Weight and Height Measurements

Each subject's body weight in kilograms and body height in meters was measured while subjects were wearing an examining gown and no shoes. Body weight was measured to the nearest 0.1 kg with portable electronic digital scales (Tanita BWB-800S, Arlington Heights, IL). Body height was measured using a vertical wall-mounted stadiometer (Tanita HR-100) and was recorded to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided by height in

meters squared. Obesity is defined as  $\text{BMI} \geq 30.0 \text{ kg/m}^2$  and overweight is defined as  $\text{BMI} \geq 25.0 - < 30.0 \text{ kg/m}^2$  (37).

#### Waist Circumference and Waist-to-Hip Ratio

WC and HC were taken with a non-elastic tape measure. WC was measured at the smallest circumference between the costal margin and the iliac crest, and HC was measured at the widest circumference between the waist and the thigh. WHR was calculated as WC divided by HC. Central obesity was defined as  $\text{WC} \geq 102 \text{ cm}$  in men and  $\geq 88 \text{ cm}$  for women (38).

#### Bioelectrical Impedance Analysis

A BIA analyzer (BIA Quantum II; RJL Systems, Detroit, MI) was used to measure resistance (R) and reactance (Xc) at 50 kHz frequency. All subjects were asked to refrain from eating, drinking, and exercising for 6 h before testing. Participants were asked to urinate within 30 min of the test and not to consume alcohol within 48 h or use diuretics within 7 days of the test. Female subjects who perceived they were retaining water due to their menstrual cycle were not tested and were missing from the BIA analysis. Subjects were placed in a supine position with arms and legs abducted approximately  $45^\circ$  to each other, assuring no contact between the thighs and between the arms and trunk. Shoes and socks were removed, and contact areas were scrubbed with alcohol immediately before electrode placement. Source electrodes were placed proximal to the phalangeal–metacarpal joint on the dorsal surfaces of the right hand and distal to the transverse arch on the superior surface of the right foot. Sensor electrodes were placed at the midpoint between the distal prominence of radius and ulna of the right wrist and between the medial and lateral malleoli on the right ankle. R and Xc were recorded to the nearest ohm ( $\Omega$ ). The following fat-free mass (FFM) prediction equations validated for Mexican-Americans (39) were applied to individual BIA resistance data in order to estimate FFM for each subject:

$$\text{Men: FFM} = -10.68 + 0.65 \text{ height}^2/\text{resistance} \\ + 0.26 \text{ weight} + 0.02 \text{ resistance}$$

$$\text{Women: FFM} = -9.53 + 0.69 \text{ height}^2/\text{resistance} \\ + 0.17 \text{ weight} + 0.02 \text{ resistance}$$

where FFM is measured in kg,  $\text{height}^2/\text{resistance}$  in  $\text{cm}^2/\Omega$ , and resistance in  $\Omega$ . Body fat mass (FM) and percent body fat (%BF) were calculated as follows:

$$\text{FM (kg)} = \text{body weight (kg)} - \text{FFM (kg)}$$

$$\% \text{BF} = [\text{FM (kg)} / \text{body weight (kg)}] \times 100$$

Obesity was defined as  $\% \text{BF} > 25$  and  $> 30$  in men and women, respectively (40,41).

#### Serum Leptin Concentration

Each participant was asked to provide a fasting blood sample when scheduled to arrive at the Student Health Services. Using standard, sterile phlebotomy procedures, a blood specimen was drawn from the antecubital vein into a tube with no anti-coagulant. Blood was allowed to clot at room temperature for 30 min and then centrifuged at  $3000 \times g$  for 15 min. Serum was aliquoted into 2-mL cryo-vials and stored at  $-70^\circ\text{C}$  until analysis. Quantitative measurement of leptin in serum was performed using a leptin enzyme immunoassay kit (ELISA) (Diagnostic Systems Laboratories, Inc., Webster, TX), according to the manufacturer's instructions. Briefly, 25  $\mu\text{L}$  of the standards, controls, and serum samples were dispensed into the appropriate wells. Using a semi-automatic dispenser, 100  $\mu\text{L}$  of the assay buffer E was added to each well. The well was incubated, shaking at fast speed (500–700 rpm) on an orbital microplate shaker, at room temperature ( $\sim 25^\circ\text{C}$ ) for 2 h. Each well was aspirated and washed five times with wash solution using an automatic microplate washer (1575 Immunowash Microplate Washer; Bio-Rad Laboratories, Hercules, CA) and blotted dry by inverting the plate on absorbent material. The antibody–enzyme conjugate concentrate was diluted in the solution and 100  $\mu\text{L}$  of the diluted solution was added to each well of the microtiter plate using a semi-automatic dispenser. The wells were incubated, shaking at a fast speed (500–700 rpm) on an orbital microplate shaker, at room temperature for 1 h. The wells were aspirated and rinsed five times with wash solution using the automatic microplate washer and blotted dry by inverting the plate on absorbent material. Using a semi-automatic dispenser, 100  $\mu\text{L}$  of tetramethylbenzidine chromogen solution was added to each well. Each well was incubated, shaking at a fast speed (500–700 rpm) on an orbital microplate shaker, at room temperature ( $\sim 25^\circ\text{C}$ ) for 10 min. Exposure to direct sunlight was avoided; 100  $\mu\text{L}$  of the stopping solution (0.2 M sulfuric acid) was added to each well using a semi-automatic dispenser. Finally, using a microplate reader (Benchmark Plus System; Bio-Rad Laboratories) the degree of enzymatic turnover of the substrate was determined by dual wavelength absorbance measurement at 450 and 620 nm. The absorbance measured is directly proportional to the concentration of human leptin present. A set of human leptin standards was used to plot a standard curve of absorbance vs. human leptin concentration from which the human leptin concentration in the serum was calculated. Serum leptin concentration was expressed in ng/mL. Hemolyzed and lipemic specimens were not used because these specimens may give false values. In this assay, the intra-assay precision (% coefficient of variation) using ten replicates of three subjects was 8.1% (2.77 ng/mL), 6.6% (67.79 ng/mL) and 4.2% (143.77 ng/mL);

the inter-assay precision from five different runs of three subjects was 8.2%, 2.6%, and 3.1% at concentrations of 2.57 ng/mL, 64.58 ng/mL, and 124.59 ng/mL, respectively. These results are comparable to those found in similar studies using either radioimmunoassay (8,19,20,26,31,32,42) or ELISA (43) methodology.

### Statistical Analysis

All statistical analyses were performed using STATA 8 (College Station, TX). Non-normally distributed variables according to the Wilk-Shapiro test were transformed after identifying the function that would transform the original variable into a normally distributed variable. Serum leptin concentration was non-normally distributed and was log transformed. Measures of central tendency and variability were computed accordingly.

Statistical analyses are presented by gender and included Mann-Whitney *U* test for independent samples to compare the medians between groups, and Spearman correlation coefficients (*rho*) for measuring the correlation between serum leptin concentration and each independent variable. Partial Spearman correlation coefficients (partial *rho*) are reported adjusting these correlation coefficients for gender and adiposity (FM measured in kg). Fisher's *z* transformation was used to compute the significance of the difference between correlation coefficients. In addition, we performed multiple linear regression analysis using backwards elimination with the log of serum leptin concentration as the dependent variable to create a predictive model of serum leptin concentration for Mexican-Americans. The following independent variables were assessed: age, body weight, body height, BMI, PBF, FM, FFM, WC, HC, and WHR. Effect modification was expected to occur between sex and potential determinants, so the analyses were performed separately for women and men (11). Diagnostic measures including influence of collinearity statistics were examined.

Power estimation for the regression model was confirmed using the method of Hsieh et al. (44). We also report the multiple regression correlation coefficient ( $R^2$ ) as a measure of the proportion of variability of serum leptin concentration explained by the independent variables in the multiple regression model. To test whether the equations adequately predict serum leptin concentration in our entire study sample we randomly split the dataset into two in order to a) derive predictive equations in one dataset, and b) predict serum leptin concentration in the other dataset. The equations effectively predicted serum leptin concentration with <8% difference compared to the final predictive equations.

Statistical significance was set using a type I error level of 0.05. For convenience and comparability with previous authors, summary statistics are presented as mean  $\pm$  standard deviation in addition to median and interquartile range for non-normally distributed variables.

### Results

Descriptive statistics of the study variables for men and women are shown in Table 1. Approximately 53% of participants were either overweight (27.6%) or obese (24.7%) based on BMI, whereas all participants were considered obese based on body fatness estimated by BIA (data not shown). In the whole group of subjects, median serum leptin concentration was  $32.5 \pm 51.4$  ng/mL. Despite similar values of BMI by gender, median serum leptin concentrations were higher in women compared with men ( $48.1 \pm 59.7$  ng/mL vs.  $10.6 \pm 17.5$  ng/mL;  $p < 0.001$ ). Age, BMI, and HC had similar median values among men and women. Men had statistically significantly higher body weight, body height, WC, WHR, FFM, FM, and PBF than their female counterparts. Table 2 shows that men and women in higher BMI categories had higher median serum leptin concentration.

**Table 1.** Descriptive statistics of demographic, anthropometric, and hormonal parameters in 352 participants

| Variable                 | Median (iqr)       |                      | Mean ( $\pm$ SD)   |                      |
|--------------------------|--------------------|----------------------|--------------------|----------------------|
|                          | Men <i>n</i> = 110 | Women <i>n</i> = 242 | Men <i>n</i> = 110 | Women <i>n</i> = 242 |
| Age (years)              | 21 (6)             | 21 (5)               | 22.1 $\pm$ 3.5     | 22.1 $\pm$ 3.6       |
| BW (kg)                  | 79.5 (27.3)        | 62.8* (21.9)         | 83.9 $\pm$ 18.1    | 67.1 $\pm$ 16.9      |
| BH (cm)                  | 174.0 (8.8)        | 159.8* (8.2)         | 174.5 $\pm$ 6.1    | 160.2 $\pm$ 5.9      |
| BMI (kg/m <sup>2</sup> ) | 26.5 (7.5)         | 24.5 (7.7)           | 27.5 $\pm$ 5.3     | 26.1 $\pm$ 6.3       |
| WC (cm)                  | 89.0 (19.5)        | 78.8* (17.3)         | 90.2 $\pm$ 12.1    | 81.3 $\pm$ 13.9      |
| HC (cm)                  | 103.0 (13.2)       | 101.5 (14.9)         | 104.1 $\pm$ 10.1   | 103.6 $\pm$ 11.9     |
| WHR                      | 0.86 (0.07)        | 0.77* (0.09)         | 0.86 $\pm$ 0.05    | 0.78 $\pm$ 0.07      |
| FFM (kg)                 | 46.2 (11.8)        | 32.4* (10.9)         | 47.9 $\pm$ 9.2     | 34.0 $\pm$ 8.2       |
| FM (kg)                  | 34.3 (15.5)        | 30.3* (11.1)         | 36.0 $\pm$ 10.9    | 33.2 $\pm$ 9.7       |
| PBF (%)                  | 43.2 (7.0)         | 49.2* (5.4)          | 42.6 $\pm$ 5.7     | 49.1 $\pm$ 3.7       |
| Serum leptin (ng/mL)     | 10.6 (17.5)        | 48.1* (59.7)         | 17.4 $\pm$ 18.5    | 60.8 $\pm$ 46.6      |

BW, body weight; BH, body height; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist/hip ratio; FFM, fat-free mass; FM, fat mass; PBF, percent body fat; iqr, interquartile range; SD, standard deviation.

\* $p < 0.001$ ; men vs. women using Mann-Whitney *U* test.

**Table 2.** Serum leptin concentration in 352 participants based on BMI

| BMI group           | Men ( <i>n</i> = 110) |                         |                  | Women ( <i>n</i> = 242) |                           |                  |
|---------------------|-----------------------|-------------------------|------------------|-------------------------|---------------------------|------------------|
|                     | <i>n</i>              | Median (iqr)            | Mean ( $\pm$ SD) | <i>n</i>                | Median (iqr)              | Mean ( $\pm$ SD) |
| BMI <18.5           | 2                     | 4.02 (5.2)              | 4.02 (3.71)      | 7                       | 13.45 (15.6)              | 17.62 (8.45)     |
| 18.5 $\leq$ BMI <25 | 36                    | 5.79 <sup>‡</sup> (6.4) | 6.88 (4.34)      | 123                     | 29.01 <sup>†</sup> (29.6) | 33.63 (20.73)    |
| 25 $\leq$ BMI <30   | 35                    | 8.54 <sup>¶</sup> (7.3) | 13.3 (14.9)      | 62                      | 65.71 <sup>¶</sup> (37.6) | 68.85 (27.72)    |
| BMI $\geq$ 30       | 37                    | 29.24* (17.8)           | 32.12 (21.60)    | 50                      | 107.30* (48.1)            | 112.39 (39.78)   |

All differences using Mann-Whitney *U* test

\**p* <0.001; BMI  $\geq$ 30 vs. 25  $\leq$  BMI <30.

¶*p* <0.001; 25  $\leq$  BMI <30 vs. 18.5  $\leq$  BMI <25.

‡*p* <0.05; 18.5  $\leq$  BMI <25 vs. BMI <18.5 for men.

†*p* <0.001; 18.5  $\leq$  BMI <25 vs. BMI <18.5 for women.

Table 3 reports the Spearman correlation coefficients for men and women between serum leptin concentration and independent variables. Prior to adjustment for FM measured in kg, most anthropometric variables were significantly correlated with serum leptin concentration and FM was most strongly correlated among men ( $\rho = 0.811$ ,  $p < 0.001$ ) and women ( $\rho = 0.818$ ,  $p < 0.001$ ). After controlling for FM in kg, no variables were significantly correlated with serum leptin concentration among men, whereas among women BMI (partial  $\rho = 0.214$ ,  $p < 0.001$ ) and HC (partial  $\rho = 0.201$ ,  $p < 0.01$ ) were significantly correlated with serum leptin concentration.

Because of the high correlation between BMI and WC ( $r = 0.82$ ,  $p < 0.001$ ) and BMI and FM (0.93,  $p < 0.001$ ), we did not examine these variables simultaneously in any regression model due to multicollinearity. However, BMI was included separately as independent variable in every model. Table 4 shows correlation matrix of independent variables examined for potential collinearity. The logarithm

of serum leptin concentration was significantly predicted by PBF in men and by PBF, WC, and HC in women (Table 5). These variables explained approximately 42% of the variance of logarithm of serum leptin concentration in men and approximately 65% of the variance of logarithm of serum leptin concentration in women. Substituting PBF with FM did not materially change the results.

## Discussion

We addressed the question of whether serum leptin concentrations are related to body fat distribution and adiposity as measured by BIA in a large sample of Mexican-American college students. To our knowledge, no previous study has examined the correlation of serum leptin concentrations with adiposity assessed by a measure other than BMI or skinfold thickness in Mexican-Americans.

Our data showed that serum leptin concentrations are highly correlated with body fatness expressed as FM in kg confirming previous results that degree of adiposity is a key determinant of leptin concentration (19,20,26,31,42). Serum leptin concentrations were positively correlated with body fatness in both men and women, although women had the higher median serum leptin concentration. This finding is in agreement with other studies showing that women have higher leptin concentrations than men at any level of adiposity (19,20,31,43). In a study of Mexican-Americans where the sum of triceps and subscapular skinfold thickness were used to assess overall adiposity, the correlations of serum leptin concentration in both men and women were higher with BMI than with the sum of skinfold thicknesses after adjustment for age (31). Conversely, our data showed a slightly higher but not statistically significant difference in the correlation coefficients of serum leptin concentration with FM compared to serum leptin concentration with BMI in both men and women prior to controlling for adiposity measured as FM in kg ( $\rho = 0.811$  vs.  $\rho = 0.766$ ,  $p = 0.09$ , and  $\rho = 0.818$  vs.  $\rho = 0.804$ ,  $p = 0.12$ , respectively). In addition, we found that adiposity expressed as

**Table 3.** Spearman correlation coefficients between serum leptin concentration and independent variables

| Variable                 | Men    |                             | Women  |                             |
|--------------------------|--------|-----------------------------|--------|-----------------------------|
|                          | $\rho$ | Partial $\rho$ <sup>1</sup> | $\rho$ | Partial $\rho$ <sup>1</sup> |
| Age (years)              | 0.183  | -0.068                      | 0.097  | 0.001                       |
| BW (kg)                  | 0.725* | -0.099                      | 0.778* | 0.083                       |
| BH (m)                   | 0.045  | -0.204                      | 0.016  | -0.117                      |
| BMI (kg/m <sup>2</sup> ) | 0.766* | 0.058                       | 0.804* | 0.214*                      |
| WC (cm)                  | 0.729* | -0.097                      | 0.777* | 0.127                       |
| HC (cm)                  | 0.739* | -0.016                      | 0.775* | 0.201**                     |
| WHR                      | 0.489* | -0.107                      | 0.456* | 0.017                       |
| FFM (kg)                 | 0.422  | -0.099                      | 0.651  | 0.084                       |
| PBF (%)                  | 0.607* | 0.086                       | 0.390* | 0.052                       |
| FM (kg)                  | 0.811* | —                           | 0.818* | —                           |

BW, body weight; BH, body height; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist-to-hip ratio; PBF, percent body fat; FM, fat mass;  $\rho$ , Spearman correlation coefficient.

<sup>1</sup>Partial Spearman correlation coefficient adjusted for adiposity (FM measured in kg).

\**p* <0.001.

\*\**p* <0.01.

**Table 4.** Correlation matrix of independent variables examined for potential collinearity

|              | PBF    | BMI    | WC     | HC      | WHR    | FM     |
|--------------|--------|--------|--------|---------|--------|--------|
| <b>Men</b>   |        |        |        |         |        |        |
| PBF          | 1.0000 |        |        |         |        |        |
| BMI          | 0.5061 | 1.0000 |        |         |        |        |
| WC           | 0.4923 | 0.9380 | 1.0000 |         |        |        |
| HC           | 0.3897 | 0.5889 | 0.5366 | 1.0000  |        |        |
| WHR          | 0.2754 | 0.3660 | 0.4819 | −0.1182 | 1.0000 |        |
| FM           | 0.7179 | 0.9210 | 0.9024 | 0.8235  | 0.3405 | 1.0000 |
| <b>Women</b> |        |        |        |         |        |        |
| PBF          | 1.0000 |        |        |         |        |        |
| BMI          | 0.4387 | 1.0000 |        |         |        |        |
| WC           | 0.3499 | 0.9042 | 1.0000 |         |        |        |
| HC           | 0.3060 | 0.6471 | 0.7137 | 1.0000  |        |        |
| WHR          | 0.1413 | 0.1580 | 0.2267 | 0.0867  | 1.0000 |        |
| FM           | 0.4838 | 0.9489 | 0.9348 | 0.9290  | 0.1720 | 1.0000 |

PBF, percent body fat; BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist/hip ratio; FM, fat mass.

FM in kg was a significant predictor of serum leptin concentration in both Mexican-American men and women.

Several studies have investigated the relationship of body fat distribution with leptin concentrations (25–32,45). Surprisingly, our data show that there was no statistically significant difference in HC values between men and women, although WC was larger in men than in women. In agreement with studies of whites and African-Americans (42) and of Mexican-Americans (31), our data showed that serum leptin concentration is not a function of a specific pattern of body fat distribution in men, although we observed a statistically significant correlation of HC with serum leptin concentration in women even after adjusting for fat mass measured in kg. It is interesting to note that in our sample, gynoid pattern determined by WHR  $\geq 1.0$  for men and  $\geq 0.8$  for women (38) was the most prevalent pattern of body fat distribution in both men and women (92% and 63%, respectively).

In agreement with a study in Asian individuals (20), we found that HC helped to predict serum leptin concentration in women. However, our data showed that both HC and WC were predictors of serum leptin concentration in women. These results suggest there is no specific body fat distribution pattern determining serum leptin concentration in both Mexican-American men and women.

In this study we performed the statistical analysis in two distinct groups, men and women, because we found evidence of effect modification by gender. The sample size was large enough to provide the necessary power for gender-based analysis.

This study was not without limitations. Although the study population was relatively large, it was a convenience sample of college students at UTB/TSC. Therefore, our sample may not be representative of Mexican-Americans. Considering the fact that the study participants were students 18–30 years old, we were not able to investigate the effect of age in other age groups. The discrepancy

between BMI values and body fatness measured by BIA in both men and women is of concern. We hypothesize the occurrence of BIA- and BMI-related reasons for this finding. In the former, the assessment of adiposity was performed using validated equations for BIA in Mexican Americans. BIA equations tend to overestimate adiposity in lean individuals and underestimate adiposity in obese individuals (39). In the latter, it has been shown that specific BMI cutoff points should be set for different ethnic groups (46) due to differences in average height among groups. For instance, lower BMI cutoff points have been proposed for Mexicans (47) and Asians (48,49). It is important to note that the mean height of our study population was lower than the average of Americans at same age and gender (50). Therefore, taken together, it seems that we cannot rule out misclassification bias. Other limitations are the lack of information on smoking status, diet and alcohol intake, lactation status, and use of oral contraceptives, as well as physical activity levels.

In summary, the findings of our study that serum leptin concentrations were higher in women than men are in

**Table 5.** Multiple linear regression analysis with backwards elimination of log of serum leptin concentration

| Independent variable                   | Coefficient | Standard error | <i>p</i> value |
|----------------------------------------|-------------|----------------|----------------|
| <b>Men (<math>R^2 = 42.3</math>)</b>   |             |                |                |
| PBF                                    | 0.10        | 0.012          | <0.001         |
| Age                                    | 0.02        | 0.007          | 0.08           |
| Constant                               | −1.754      | 0.452          | 0.001          |
| <b>Women (<math>R^2 = 65.4</math>)</b> |             |                |                |
| PBF                                    | 0.03        | 0.009          | <0.001         |
| WC                                     | 0.02        | 0.005          | <0.001         |
| HC                                     | 0.03        | 0.005          | <0.001         |
| Age                                    | 0.01        | 0.004          | 0.1            |
| Constant                               | −2.241      | 0.265          | <0.001         |

PBF, percent body fat; WC, waist circumference; HC, hip circumference;  $R^2$ , multiple regression correlation coefficient.

agreement with the literature. We demonstrated that higher serum leptin concentrations were correlated with the physiological higher adiposity seen in Mexican-American women. In addition, BMI, HC, and WC are associated with serum leptin concentration in Mexican-American women even after adjusting for fat mass measured in kg. Therefore, it seems there is no preferential pattern of body fat distribution related to serum leptin concentration in Mexican-Americans. We suggest that BMI alone should not be used in evaluating the association of serum leptin concentration with body fatness in Mexican-Americans. Further studies using more accurate methods of body composition should be carried out to confirm our findings. Also, we suggest that further studies be conducted to evaluate if our predictive equation is applicable to similar populations of Mexican Americans.

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**Insulin Resistance and Breast Cancer**

Maureen Sanderson, PI

The primary purpose of this proposed pilot study is to investigate the association between insulin resistance and breast cancer risk. We hypothesize that 1) insulin resistance, defined as high levels of insulin and glucose or type 2 diabetes, will be positively associated with breast cancer, and 2) the insulin resistance-breast cancer association will be more pronounced among women with abdominal obesity and high levels of estradiol (E2). The specific aims of the proposed case-control study are: 1) to obtain information on type 2 diabetes, waist and hip circumference, body mass index, body fat content, birth weight, age at which adult height was achieved, diet, physical activity, and weight gain, and to collect pre-diagnostic blood, 2) to assay blood for E2, sex hormone-binding globulin, insulin, glucose, and triglycerides, and 3) to perform statistical analyses to assess the association between insulin resistance and breast cancer risk, while accounting for confounding and interaction. This proposed study will be conducted in three mammographic centers. We plan to recruit 390 incident breast cancer cases and 390 control women. Breast cancer cases will be those women identified as having breast cancer through diagnostic mammography prior to undergoing treatment. Control women will be those women who are cancer free through screening mammography. In addition, control women will be at low risk of breast cancer defined as having no previous lesions that place her at higher than minimal risk, and no first-degree relative with a history of breast cancer or other hormone-related cancer. Insulin resistance may be associated with breast cancer, and may help explain the elevated risk of breast cancer among certain ethnic groups. Despite being at greater risk of insulin resistance, Hispanic women have a relatively low incidence of breast cancer. This proposed study may be useful in identifying factors associated with decreased breast cancer risk among Hispanic women.

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**Cancer Disparities, Reporting and Prevention among Texas-Mexico Border Hispanics**

Maureen Sanderson, PI

Specific aims of the Cancer Disparities, Reporting and Prevention among Texas-Mexico Border Hispanics Core are: 1) to identify cancers for which health disparities exist in this population, 2) to develop a regional cancer registry for the Lower Rio Grande Valley (LRGV) of Texas, 3) to conduct epidemiological studies of these cancers, and 4) to develop and test culturally sensitive primary and secondary interventions to reduce the burden of cancer in this population. We received an R21 from the National Cancer Institute to assess cancer disparities by utilizing data from the Texas Cancer Registry to investigate the association between neighborhood socioeconomic status and cervical cancer survival. We received funding from the Texas Cancer Council to improve cancer reporting by piloting data collection from pathology labs in the LRGV and in the Mexican state of Tamaulipas. We completed a pilot study funded by the National Center for Minority Health and Health Disparities and are currently funded by the Department of Defense to conduct a clinic-based case-control study of the association between insulin resistance and breast cancer. We are currently conducting a cohort study to determine knowledge gaps and information needs of women who are diagnosed with high-risk human papillomavirus (HR-HPV) and therefore at high risk of cervical cancer. To date we have completed in-depth interviews with health care providers to explore their attitudes and perceptions about women who have HR-HPV and the perceived needs of HR-HPV positive women. We have also completed in-depth interviews with women who were diagnosed with HR-HPV to identify knowledge gaps, attitudes, related behaviors and the perceived impact of a HR-HPV diagnosis. We are currently conducting focus groups with women and men to assess the acceptability of: 1) an informational brochure which some of the women will receive as an

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intervention, 2) self-collection of samples, and 3) partner participation in interviews and self-collection of samples. Upon completion of the focus groups we will begin conducting initial telephone interviews with women who have been diagnosed with HR-HPV, and follow-up interviews at 6 and 12 months. Information will be used to develop meaningful interventions for women with and without HPV and provide health care professionals with appropriate educational materials for patients. We have received funding from the Centers for Disease Controls and Prevention to develop a secondary intervention for colorectal cancer screening among Texas-Mexico border residents. Results of these studies will help us identify cancer disparities, improve cancer reporting, and develop interventions in an attempt to prevent cancer in the LRGV.

**Serum Leptin Values in Mexican Americans: Association with  
Body Fat, Body Mass Index, and Obesity**

Gerson Peltz, PI

The role of leptin in human obesity remains controversial. Leptin, the protein encoded by the *ob* gene, is produced in adipose tissue and released into circulation. Leptin interacts with a number of hypothalamic neuropeptide systems to regulate both feeding behavior and energy expenditure. Serum and plasma leptin concentrations are highly correlated with adiposity and body fat stores. However, the presence of high serum or plasma leptin concentrations in most obese subjects has been interpreted to suggest that human obesity is most often associated with resistance to the actions of leptin.

In population-based studies, limited attention has been paid to the relationship of leptin concentrations with body composition measures other than body mass index. However, since body mass index does not accurately measure adiposity, the effects of adiposity on leptin concentration may be more pronounced when more reliable methods are used to measure total body fat content. Additionally, the relationship between leptin concentration with body fat distribution is inconsistent. In contrast with metabolic syndrome, it is not sufficiently clear the correlation of central obesity with leptin concentration. Studies comparing ethnic groups thus far have shown conflicting results.

The proposed pilot project will investigate a) the correlation of serum leptin concentration with body fat content using bioelectrical impedance analysis, a more accurate tool to measure adiposity, and b) the correlation of serum leptin concentration with body fat distribution. In addition, the proposed pilot project will assess body composition using bioelectrical impedance analysis in a large sample of young Mexican American adults.

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The Lower Rio Grande Valley is an area with high rates of nutrition related disorders, such as obesity and type-2 diabetes mellitus. The implementation of the proposed pilot project will be instrumental for developing further nutritional epidemiologic studies at The University of Texas at Brownsville. Along with the primary objectives, the proposed project will a) provide opportunities to enhance and expand biomedical research to undergraduate and graduate underrepresented students in order to promote awareness of biomedical careers, b) provide an excellent opportunity to develop a comprehensive community educational awareness program that will augment existing health education programs being viewed by health care workers and the general public, c) contribute to develop the infrastructure to support biomedical research and d) increase in the pipeline of students pursuing a science track leading to biomedical careers.

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**Partnership between the Texas Cancer Registry and the UTSPH-B for Assuring Timely,  
Complete and Accurate Cancer Data in the Lower Rio Grande Valley of Texas**

Maureen Sanderson, PI

The Texas Cancer Registry (TCR) is one of nine state registries that have not achieved silver or gold certification through the North American Association of Central Cancer Registries (NAACCR). The Border region has one of the lowest completeness of case ascertainment and highest percentage of death certificate only cases in the state. Delays in reporting and failure to report outpatient cases may be due to Border residents being diagnosed, treated and/or dying in Mexico never to appear on the TCR. In addition to problems related to timeliness, quality and completeness of cancer reporting, the existing Certified Tumor Registrar (CTR) workforce in Texas is aging, with few young entrants into the profession. American College of Surgeons (ACoS) facilities will be required to have a CTR performing or supervising their tumor registration activities in order to maintain ACoS certification. An increasing number of facilities must report to the TCR and many facilities, especially those in rural areas, have expressed difficulty in attracting and retaining CTRs. The goals of the proposed project which focuses on the Border region of the state are: 1) to improve cancer registration and cancer data, and 2) to build capacity for a qualified cancer registration workforce. To accomplish the first goal we (the University of Texas-Houston School of Public Health at Brownsville – UTSPH-B) are proposing to partner with the TCR, the Texas A&M Health Science Center-School of Rural Public Health (SRPH), the University of Texas Health Science Center at San Antonio Laredo campus (UTHSC-SA), and San Antonio Cancer Institute (SACI) to utilize different methods for improving cancer registration. To accomplish the second goal we are proposing to partner with the TCR, the University of Texas at Brownsville (UTB), and the UTHSC-SA Laredo campus,

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and SACI to build cancer registration capacity. Objectives of the proposed project are: 1) to pilot the feasibility of electronic pathology laboratory reporting from independent labs that perform diagnostic confirmation of cancer among Border residents, 2) to investigate the possible reporting of pathologic diagnoses for Border residents being performed across the Border, 3) to investigate the feasibility of identifying and obtaining information on Border residents with cancer who die in Mexico, 4) to train project staff to conduct cancer surveillance activities, and 5) to design a Bachelor of Science in Health Information Management degree with an emphasis in tumor registration to be offered through allied health schools. These activities will help improve the completeness of cancer case reporting and death information needed for survival analyses in the Border region, and will be replicated elsewhere in the state. The partnerships of three health science centers, an undergraduate institution, and a cancer institute with the TCR will assist in providing needed information for cancer research, prevention and control activities, and in moving the TCR closer towards achieving national gold certification. These partnerships should also lead to collaborations that will utilize data from the TCR to accurately assess the cancer burden within the state. We would like to include the Texas Cancer Council in our partnerships to improve cancer registration and to build capacity for a qualified cancer registration workforce in the Border region.

**Urinary Excretion of Phytoestrogen and Breast Cancer among Hispanic Women**

Gerson Peltz, PI

Phytoestrogen intake, measured as dietary consumption of phytoestrogens or as urinary excretion of phytoestrogens, has been found to be protective against breast cancer, especially in populations that consume large amounts of soy. Despite possessing many risk factors for breast cancer, Hispanic women have a relatively low incidence of the disease. A possible explanation for the lower risk of breast cancer among Hispanic women is their high consumption of grains rich in phytoestrogens. We hypothesize that high phytoestrogen intake, as measured by urinary excretion of phytoestrogen, will be protective against breast cancer in a population of Hispanic women. We propose to add urine collection and assessment of urinary excretion of phytoestrogen, another measure of phytoestrogen intake to the ongoing South Texas Women's Health Project, to more accurately reflect consumption of phytoestrogen-rich foods by women in our population. Specific aims of the proposed pilot project are: 1) to determine phytoestrogen intake by measuring urinary excretion of phytoestrogens on a sub-sample of 400 cases and 400 controls participating in our ongoing case-control study of breast cancer, 2) to investigate association between dietary consumption of phytoestrogen, urinary excretion of phytoestrogen, and blood levels of hormones and growth factors among controls, and 3) to evaluate whether phytoestrogen intake reduces breast cancer risk. We will add urine collection from subjects to the ongoing South Texas Women's Health Project. We will perform assays on urinary excretion of phytoestrogen on a sub-sample of 400 cases and 400 controls. We will conduct statistical analyses to evaluate phytoestrogen intake and its relation with hormones, growth factors and breast cancer. The proposed pilot project to be conducted within an ongoing case-control study will be one of very few breast cancer studies that have focused on Hispanic women. The

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identification of protective factors against breast cancer among Hispanic women may contribute to our understanding of the biological mechanisms of the disease.